Outcome of Survey on Current Standards and Implementation of Covariate Adjusted and Stratified Analyses

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On behalf of the Conditional vs Marginal Effects TF within the ASA Oncology Estimand WG

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Acknowledgements

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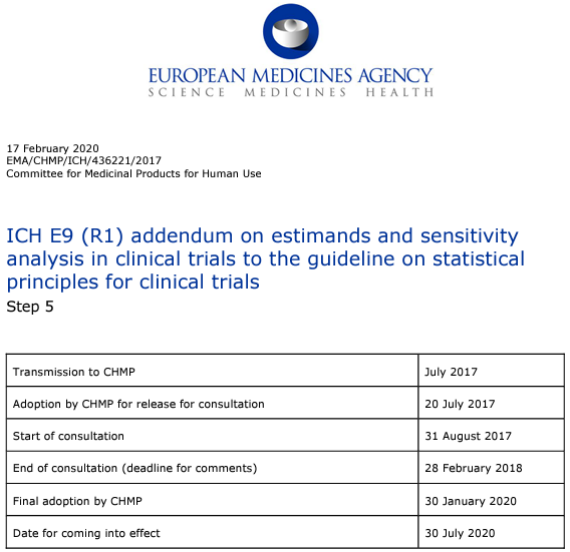
Objective

We would like to bring the complex concept and methods about conditional and marginal treatment effect into a simplified and interpretable way. Potential topics including adjusted or unadjusted analysis; stratified vs unstratified hazard ratio; collapsibility and subgroup; p-values; etc. We will give clinically relevant opinions and recommendations based on our interpretation and illustrate the idea using some case studies.

Motivation

- Given the recent release of guidelines on estimands and covariate adjustment, how is this being implemented in practice?
- Are there any existing gaps in knowledge?
- Models for time-to-event endpoints are non-linear (e.g. Cox model) – additional considerations

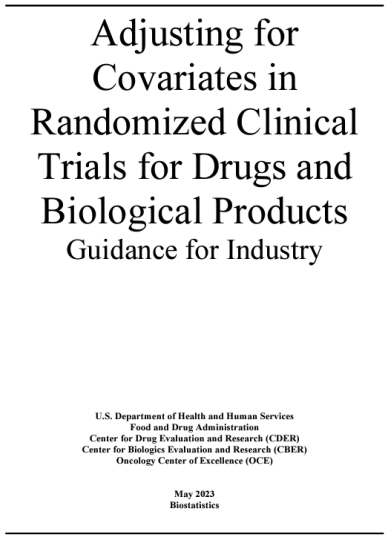


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 February 2020
EMA/CHMP/ICH/436221/2017
Committee for Medicinal Products for Human Use

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials
Step 5

Transmission to CHMP	July 2017
Adoption by CHMP for release for consultation	20 July 2017
Start of consultation	31 August 2017
End of consultation (deadline for comments)	28 February 2018
Final adoption by CHMP	30 January 2020
Date for coming into effect	30 July 2020



Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

May 2023
Biostatistics

Quick Recap of Conditional and Marginal Estimands

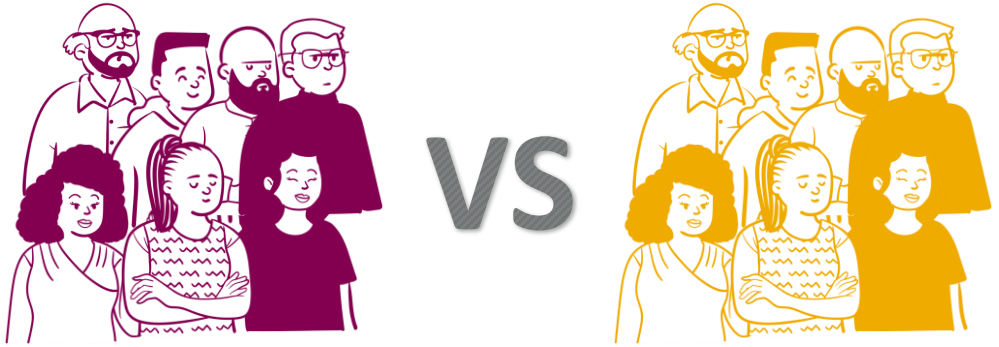
- Reserve “conditional” and “marginal/unconditional” to describe the estimand
- Unadjusted, adjusted and stratified used to describe the analysis method

Conditional estimand

Treatment effect had the patients with covariate values $\boldsymbol{X}$ taken **test treatment** vs. had they taken **control**.

More relevant interpretation for the individual patient as effect defined by the values $\boldsymbol{X}$.

Marginal estimand



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

- Conditional ≠ Marginal due to non-collapsibility of hazard ratio (summary measure)

Oncology Trials

- Traditionally, stratified Cox Model using stratification factors was and still often specified as primary analysis method
- Post-ICH E9(R1): What estimand does this target? Is that what we are truly interested in?

(Another) Quick Recap: What is a Stratified Cox model?

- Estimates separate baseline hazards for each stratum
- Constant coefficients across stratum
- The overall hazard ratio / partial likelihood is obtained by multiplying each stratum-specific partial log-likelihood

So which estimand do you think a stratified Cox model targets?

Aligning the Estimation with Estimand

- We need to be clear on what the target estimand is. Is it a conditional or marginal one?
- How we handle covariate adjustment / strata in estimation depends on the target estimand.
- From an estimation perspective: what estimand does an unstratified vs stratified analysis target?
- What challenges are usually associated with the stratified and covariate adjusted analyses?
- Are we changing our estimand when we attempt to address these challenges?

Survey Design

- The survey was hosted on SurveyPlanet.com and was active from June to July 2023.
- Survey distributed amongst Oncology Estimand WG member's networks, point-of-contacts at different companies and institutions and was also posted in the ASA Biopharm section.

Aim:

1. Better understand the current practices of covariate adjustment and stratified analysis across various sectors including academia, industry, government, non-profit organizations, contracting/consulting companies etc.

2. Identify the challenges associated with applying covariate adjustment and stratified analysis.

Characteristics of Respondents

	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%)

Majority of respondents from Confirmatory Clinical Trials working with the US in the pharmaceutical industry.

Questions

The survey included 19 questions in total which were drafted with the aim to:

1. Capture participant characteristics
2. **Understand how individuals think about the target estimand after covariate adjustment or stratification**
3. How individuals perform the selection of stratification factors/covariates
4. Understand the challenges of small-strata
5. Gather challenges associated with implementing covariate adjustment or stratification and identify any remaining gaps for addressing

Impact of Covariate Adjustment on the Estimand (Q5, Q6, Q15)

- 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
- Learning: What does unstratified analysis mean?

Different non-linear models	Do they target the same estimand?	
	Yes	No
Stratified analysis vs. unstratified analysis	61.48% (75/122)	31.97% (39/122)
covariate-adjusted analysis vs. covariate-unadjusted analysis	56.56% (69/122)	38.52% (47/122)
Remove or pool strata at interim vs. prespecified analysis at final	57.38% (70/122)	38.52% (47/122)

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)

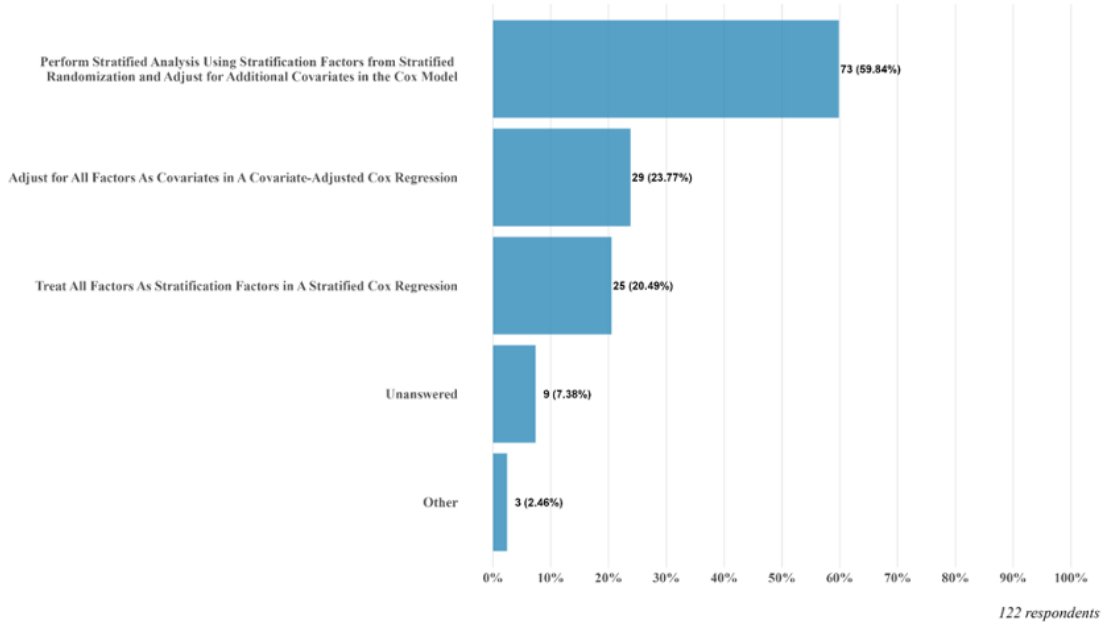
Daniel R, Zhang J, Farewell D. Making apples from oranges: Comparing noncollapsible effect estimators and their standard errors after adjustment for different covariate sets. Biometrical Journal. 2021; 63: 528–557

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

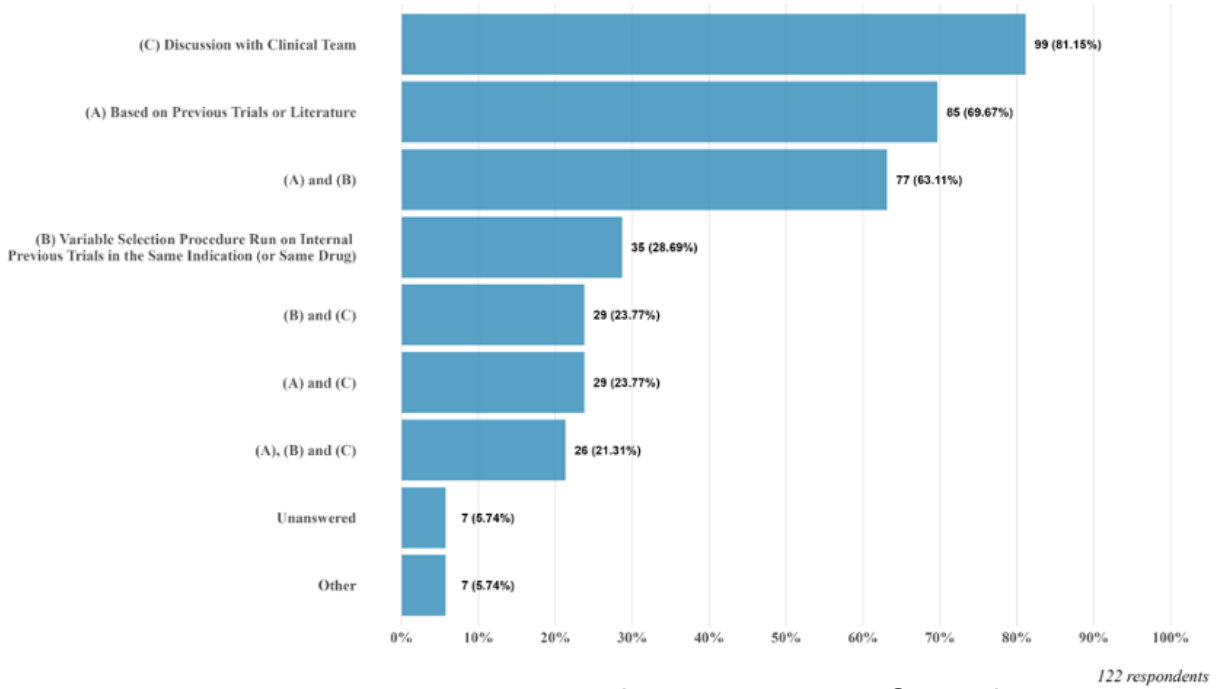
Wei, J., Xu, J., Bornkamp, B., Lin, R., Tian, H., Xi, D., … Roychoudhury, S. (2024). Conditional and Unconditional Treatment Effects in Randomized Clinical Trials: Estimands, Estimation, and Interpretation. Statistics in Biopharmaceutical Research, 1–11..

Stratification Factor / Covariate Selection (Q7,Q8,Q9)

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



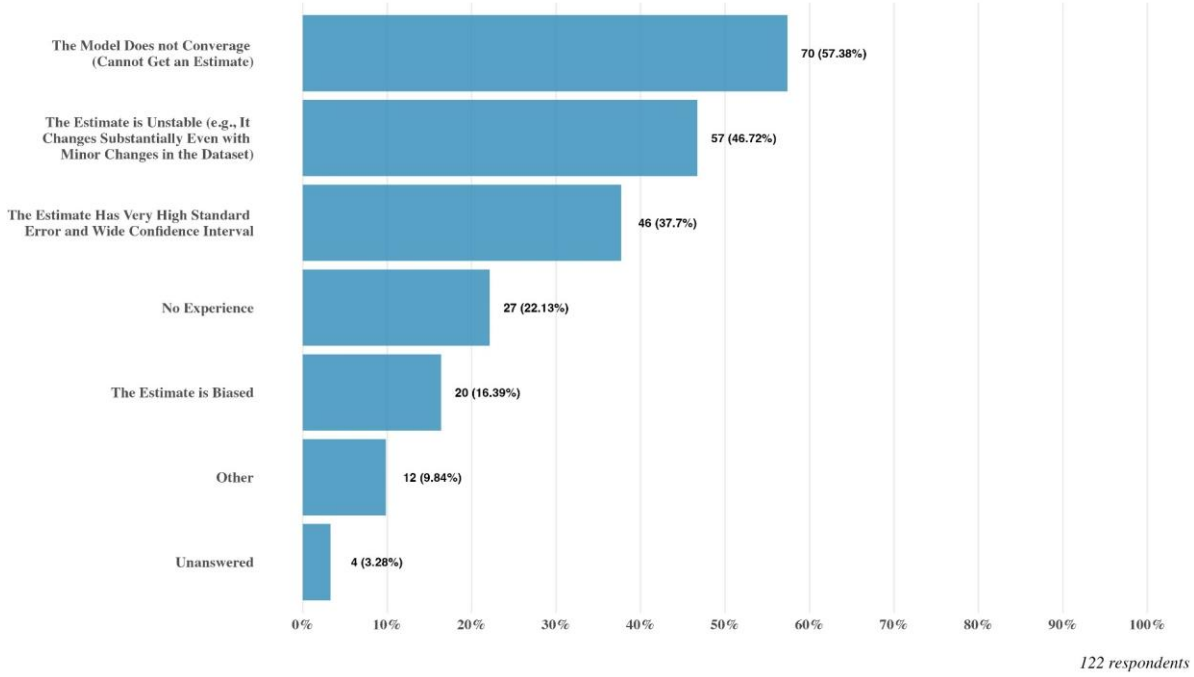
Response to Q8: In a trial with stratified randomization, how do you incorporate the stratification factors as well as other prognostic covariates in a Cox model?



Response to Q9: How are the covariates for adjustment selected for the analysis model (if covariates beyond the stratification factors are used)?

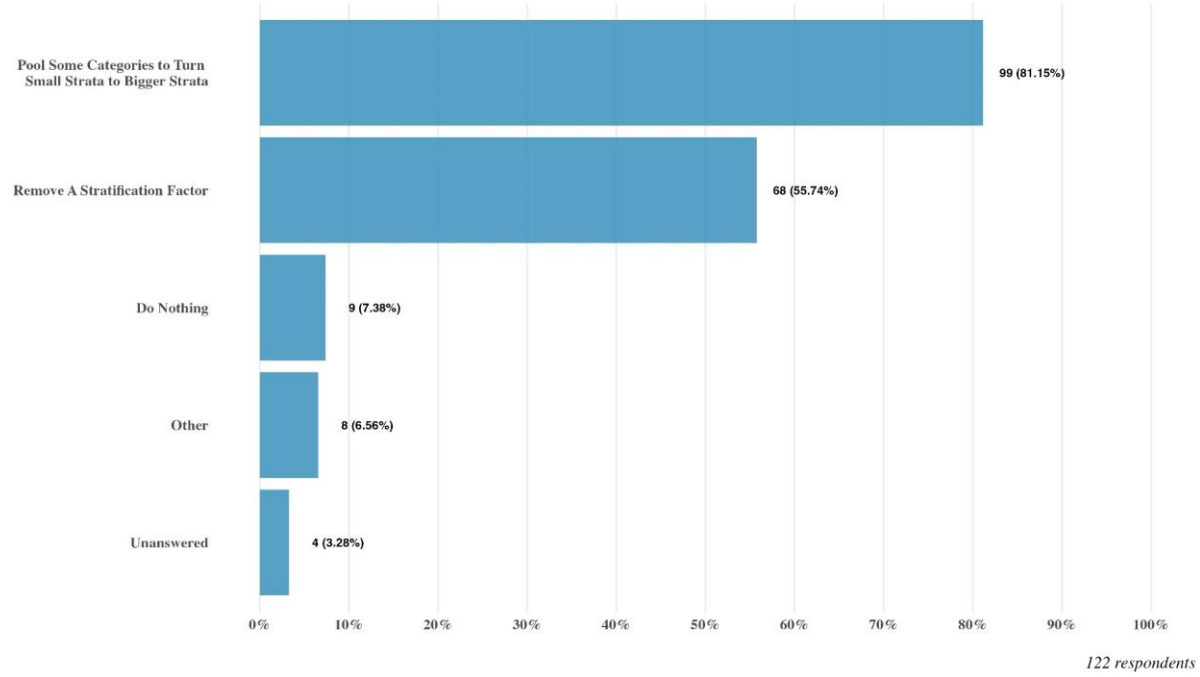
Challenges with small strata (Q10-Q14)

Response to Q10: Have you experienced challenges with small strata (e.g., strata with sparse data/small number of participants)?



- Although 16.4% of participants suggest small strata leads to biased estimates, in reality, unlikely to be systematic bias due to randomisation (imbalance due to small strata could equally favour either treatment arm)

Response to Q13: If you have experienced challenges with small strata, how do you handle them in the analysis?



- Majority pool or drop stratification factor if small strata
- Caution: this would change interpretation in a conditional estimand as your individual treatment effect has different set of characteristics

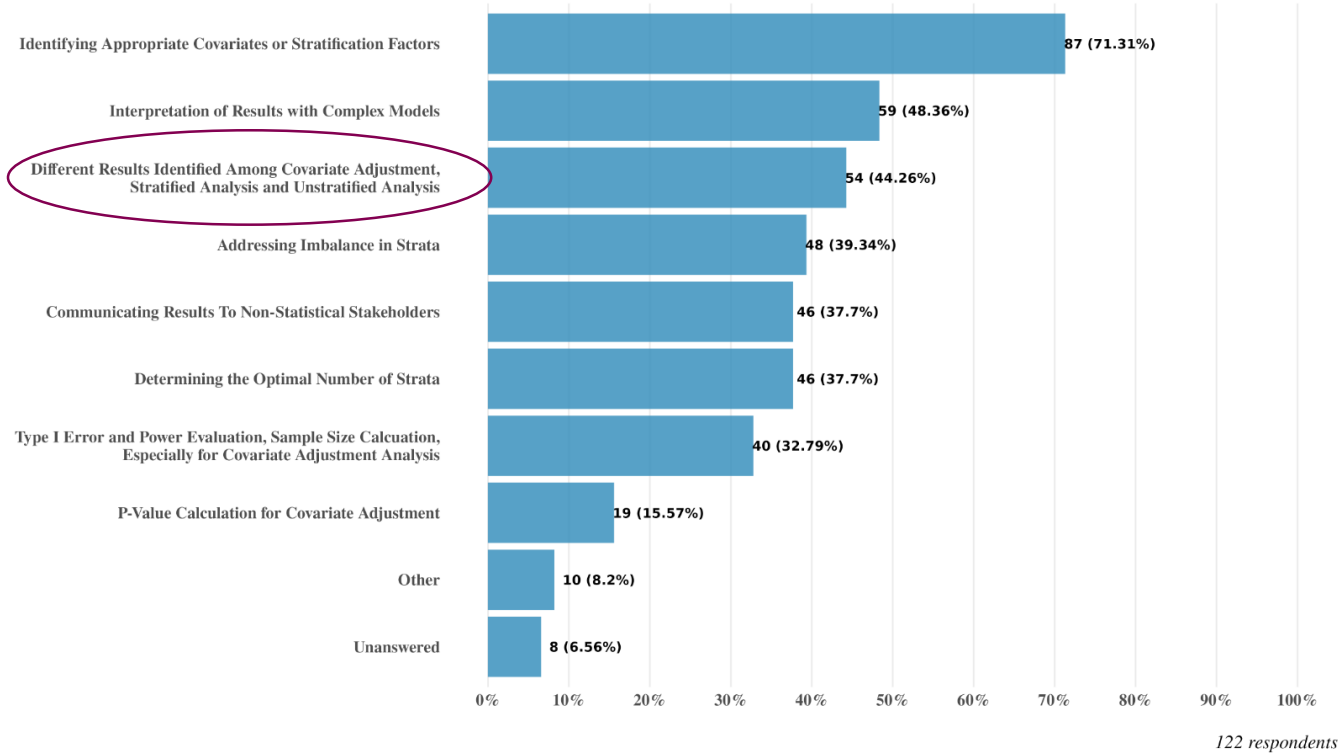
Regulatory Interactions (Q16,Q17)

- 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

Current Challenges (Q18,Q19)

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?



- Need for more training and coherent guidance
  - 59% not aware of any company wide guidance (Q19)

Limitations and 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 even following the FDA guidance in 2023 and various other papers
  - 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 (RobinCar)

Future Direction

- Collaboration/Merge into ASA BIOP Covariate Adjustment Working Group
  - Currently working together on software development to provide a validated package that tailors to the needs for covariate adjustment and stratified analysis.

- Standardization and Outreach Sub-team of the ASA BIOP working group can be leveraged to address some of the aspects highlighted in survey

- **Results of this survey soon to be submitted for publication**

Back-up: Survey Questions

Characteristics of the respondents

Q1/19: Please select the type of organization you are affiliated with:*

- a) Acedemic center (e.g. Cancer Center, Medical Schools)
- b) Pharmaceutical company / Biotechnology company
- c) Government agency
- d) Non-profit organization
- e) Contracting / Consulting company
- f) Other (please specify the name of the organization in the comment box)

Q2/19: Which drug development stage do you mainly support?*

- a) Pre-clinical
- b) Early phase exploratory stage
- c) Confirmatory stage
- d) Post-marketing

Availability of internal guidelines within the organisation

Q3/19: Does your organisation provide a company-wide or disease-unit specific internal guidance on covariate adjustment or stratified analyses?

- a) Yes - for covariate adjustment
- b) Yes - for stratified analyses
- c) Yes - for both
- d) Not that I'm aware of (skip to Q5)

Q4/19: If answered "Yes" in Q3 and the guidance is specific to certain therapeutic area(s). Select all that apply.

- a) Oncology
- b) Cardiology, Hematology, Endocrinology and Nephrology
- c) Neuroscience
- d) Infectious diseases (COVID-19 included)
- e) Immunology and Inflammation
- f) Rare Diseases, Pediatrics
- g) Other (please specify the therapeutic area in the comment box)

Does covariate adjustment or stratified analysis in a non-linear model target different estimands?

Q5/19: In non-linear models (such as Cox regression and logistic regression model), how do you approach stratified analysis and unstratified analysis in practice?

- a) They target the same estimand; if one is considered as the primary analysis, the other could be the sensitivity analysis
- b) They target different estimands (e.g. supplementary analyses)

Q6/19 : In non-linear models (such as Cox regression and logistic regression model), how do you approach covariate-adjusted analysis and covariate-unadjusted analysis in practice?

- a) They target the same estimand; if one is considered as the primary analysis, the other could be the sensitivity analysis
- b) They target different estimands (e.g. supplementary analyses)

Q15/19: If strata are removed or pooled on an ad-hoc basis just for interim analysis, do you consider this to be the same estimand as the pre-specified one for the final analysis?

- a) Yes
- b) No

How to select/include covariates or stratification factors in the model?

Q7/19: When determining factors to be adjusted in the analysis model (either included as covariates or stratification factors), do you only consider the factors used for stratified randomization?

- a) Yes
- b) No, I consider additional covariates

Q8/19: In a trial with stratified randomization, when using Cox regression, in principle, how do you incorporate stratification factors from stratified randomization as well as other prognostic covariates in the model? Select all that apply.

- a) Treat all factors as stratification factors in a stratified Cox regression
- b) Adjust for all factors as covariates in a covariate-adjusted Cox regression
- c) Perform stratified analysis using stratification factors from stratified randomization and adjust for additional covariates in the Cox model
- d) Other (please specify your approach in the comment box)

Q9/19: How the covariates for adjustment selected for the analysis model (if covariates beyond the stratification factors are used)? Select all that apply.

- a) Based on previous trials or literature
- b) Variable selection procedure run on internal previous trials in the same indication (or same drug).
- c) Discussion with clinical team
- d) Other (please specify your approach in the comment box)

Challenges with small strata

Q10/19: Have you experienced challenges with small strata (e.g., strata with sparse data/small number of participants)? Select all that apply.

- a) The model does not converge (cannot get an estimate)
- b) The estimate has very high standard error and wide confidence interval
- c) The estimate is unstable (eg, it changes substantially even with minor changes in the dataset)
- d) The estimate is biased
- e) No experience
- f) Other (specify the challenge you experienced)

Q11/19: When planning a study, how small a stratum is considered "small" in practice in terms of **number of patients** for a target probability of 0.4 of a binary endpoint (or for a continuous endpoint)?

- a) < 5
- b) <10
- c) <15
- d) Others (please specify your number in the comment box)

Q12/19: When planning a study, how small a stratum is considered "small" in practice in terms of **number of events** for time-to-event endpoint?

- a) < 5
- b) <10
- c) <15
- d) Others (please specify your number in the comment box)

Q13/19: If you have experienced challenges with small strata, how do you handle them in the analysis? Select all that apply.

- a) Remove a stratification factor
- b) Pool some categories to turn small strata to bigger strata
- c) Do nothing
- d) Other (please add the specific rule if any in the comment box)

Q14/19: Would you handle the small stratum by pre-specifing clear rules in the protocol, or on an ad-hoc basis?

- a) Pre-specify clear rules in the protocol
- b) On an ad hoc basis

Regulatory interactions

Q16/19: Have you received generally consistent feedback from multiple regulatory agencies regarding covariate adjustment or stratified analysis? Select all that apply.

- a) Too many strata
- b) Small strata
- c) Combining small strata
- d) Removing stratification factors (that were used in the stratified randomization)
- e) Too many covariates in the covariate adjusted analysis
- f) The form of covariate variables (e.g. dichotomized from a continuous variable)
- g) No
- h) Other (please specify the feedback in the comment box)

Q17/19: If you received feedback from regulatory agencies, please provide more details on what regulatory agency you have engaged (FDA/EMA/PMDA/NMPA). Select all that apply.

- a) FDA
- b) EMA
- c) PMDA
- d) NMPA
- e) Other (please specify the regulatory agencies you received feedback in the comment box)

Current challenges

Q18/19: In your experience, what are the most common challenges you have faced when implementing covariate adjustment or stratified analysis in clinical trials? Select all that apply.

- a) Identifying appropriate covariates or stratification factors
- b) Determining the optimal number of strata
- c) Addressing imbalance in strata
- d) Different results identified among covariate adjustment, stratified analysis and unstratified analysis
- e) Interpretation of results with complex models
- f) Communicating results to non-statistical stakeholders
- g) Type I error and power evaluation, sample size calcuation, especially for covariate adjustment analysis
- h) P-value calculation for covariate adjustment
- i) Other (please specify your challenges in the comment box)

Q19/19 : What resources or support would be most helpful for you in addressing the challenges of covariate adjustment and stratified analysis in clinical trials? Select all that apply.

- a) Access to comprehensive guidelines or best practices
- b) Webinars or training sessions on specific topics
- c) Case studies or examples from industry experts
- d) A platform for collaboration and discussion with fellow statisticians
- e) Consultation or mentorship from experienced professionals
- f) Access to specialized software or tools for covariate adjustment and stratified
- g) Other (please specify your needs in the comment box)

Abstract

Careful consideration is required when adjusting for covariates in non-linear models for binary and time-to-event outcomes. Specifically, a decision must be made on the estimand we're most interested in , is it a marginal or conditional one? This is further highlighted by the recent release of the FDA guidance on covariate adjustment. A further question arises out of this choice in estimand, that is, what is the appropriate estimator for the target estimand. Do we really understand what estimand is being targeted when specifying a stratified or unstratified analysis? The covariate adjustment effects task force conducted a survey with the goal of identifying the current challenges associated with applying covariate adjustment as well as the general understanding of the choice in estimand and impact on the associated analysis. We present these results along with learnings and some tentative recommendations to progress towards establishing a consensus on covariate adjustment and stratified analysis best practices.