MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Adaptive Methods in Clinical Research

Lecture 8: Estimation after Adaptive Designs

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19th September 2024

Overview

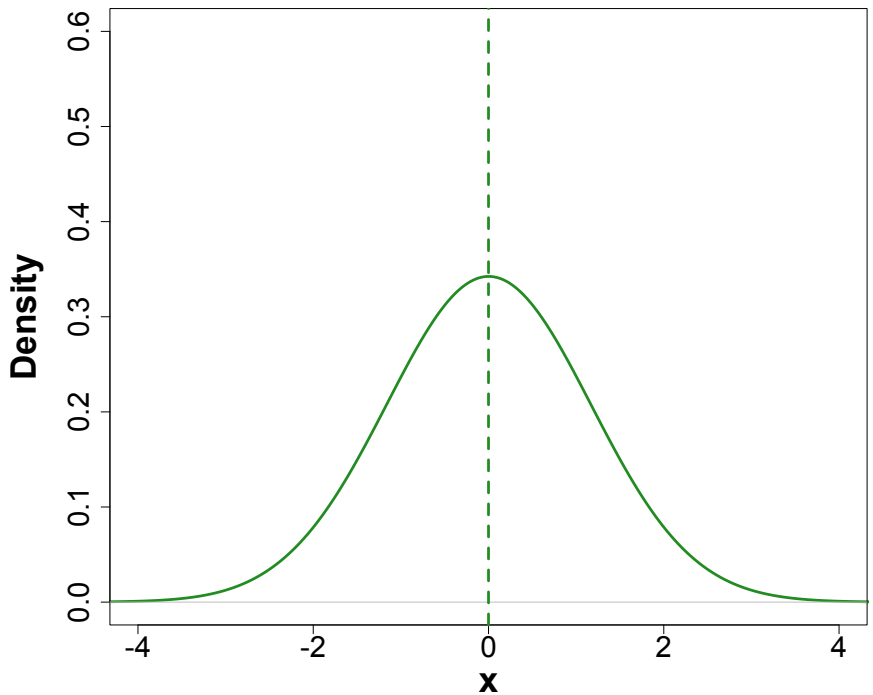
1. What are the issues with estimation after ADs?
2. Unbiased and bias-reduced point estimation
3. Adjusted confidence intervals
4. Practical aspects and guidelines

Motivation

- Appropriate estimation of treatment effects is an important part of trial validity
- Key issues for adaptive clinical trials is that the usual end-of-trial estimators can be prone to bias and confidence intervals (CIs) can have incorrect coverage (as well as other problems – see later)
  - Bias = *"A systematic tendency for the estimate of treatment effect to deviate from its true value" (FDA)*
  - Coverage = *probability that the CI contains the true unknown treatment effect of interest*
- The question of estimation of treatment effects in an adaptive clinical trial has received comparatively less attention

Motivation – point estimation

- Suppose outcome measure of experimental treatment follows a standard normal distribution
- What happens when we select the best-performing (i.e. treatment with highest observed mean) of *k* such treatments?



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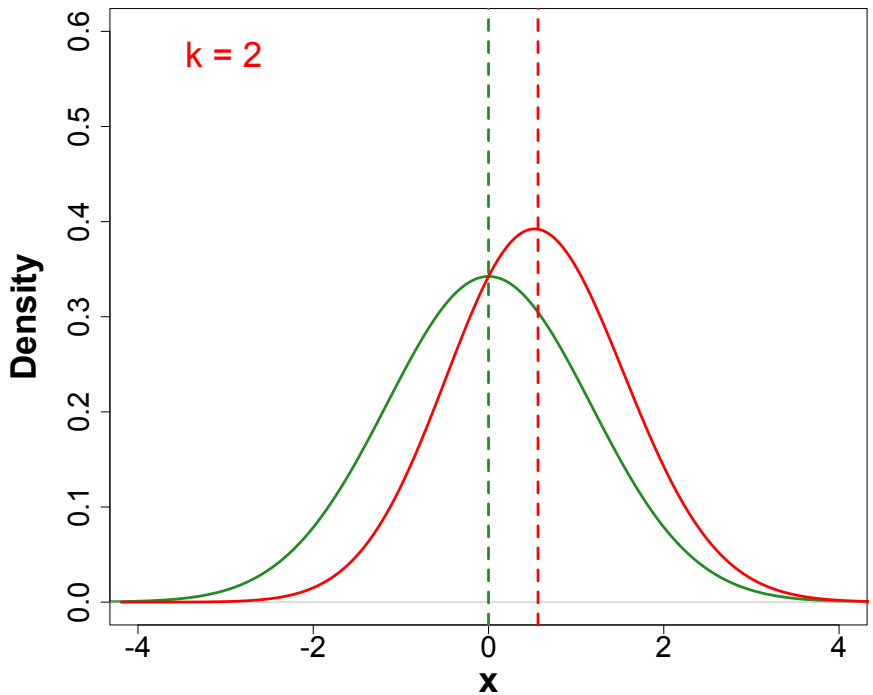

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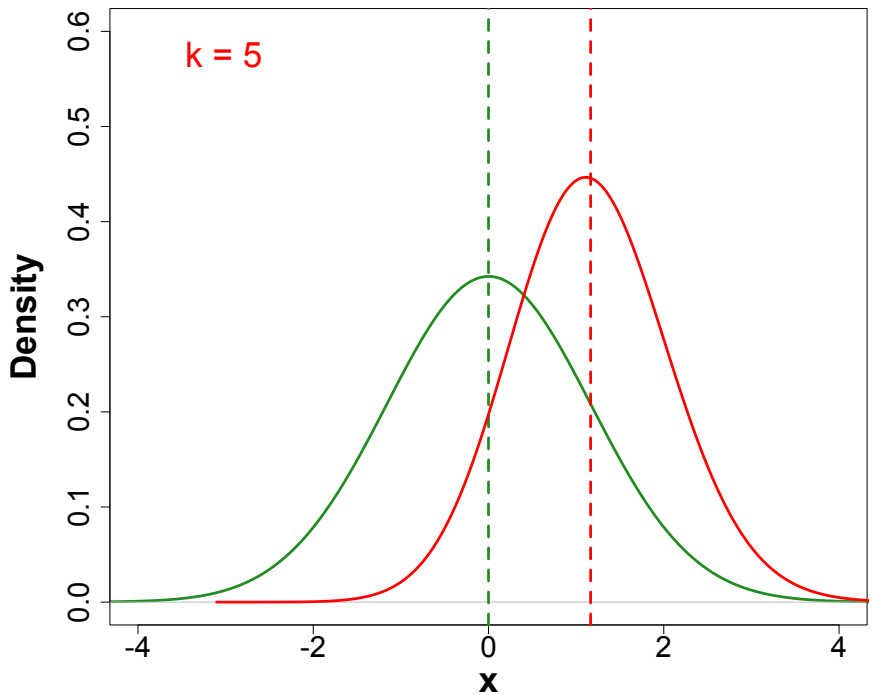

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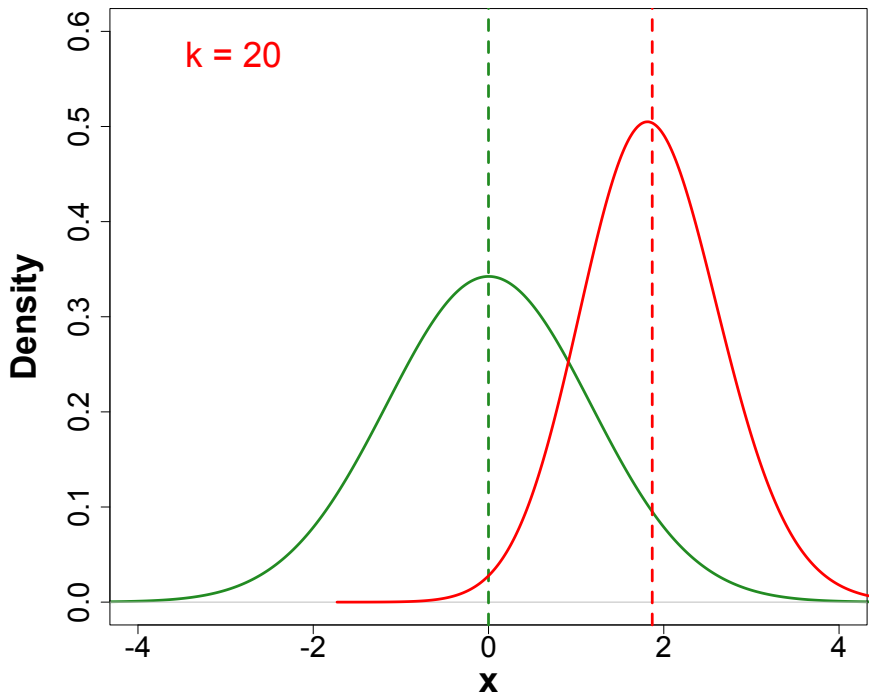

Motivation – CIs

- Consider a group sequential trial with $J = 5$ equally-spaced analyses
- Coverage probabilities for standard/naive 90% CIs for Pocock and O'Brien-Fleming boundaries:

θ	Pocock	O'Brien-Fleming
0.0	0.881	0.907
0.5	0.846	0.878
1.0	0.869	0.883
1.5	0.891	0.892
2.0	0.918	0.914

Motivation

What are the issues with biased estimation and incorrect CIs?

- Reporting substantially biased estimates for a primary outcome measure following an adaptive design can result in poor decisions
- Concern about over- or under-estimation of treatment effects affecting further research
- Impact on health economic analyses

Estimation after adaptive designs

- Question: how to best construct point estimates and CIs for the treatment effect in adaptive trials
- Lack of established methods – still an active area of research

Unbiased and bias-reduced point estimation

- Lots of methods to remove or reduce the bias in the MLE
- Two broad classes:
  1. Unbiased estimators
  2. Bias-reduced estimators
- Also distinguish been *conditionally* and *unconditionally* unbiased estimators:
  - *Unconditionally* unbiased if it is unbiased when averaged across all possible realizations of an adaptive trial
  - *Conditionally* unbiased if it is unbiased only conditional on the occurrence of a subset of trial realizations
  - E.g. one might be interested in an estimator only conditional on a particular arm being selected at an interim analysis

Bias and MSE

- Mean bias of an estimator $\hat{\theta}$ of the parameter θ is

$$\text{bias}(\hat{\theta}) = \text{E}(\hat{\theta}) - \theta$$

- An estimator that has mean bias identically equal to 0 (for all possible values of $\theta \in \Theta$) is said to be *mean-unbiased*

- The *mean squared error* (MSE) is

$$\text{mse}(\hat{\theta}) = \text{E}(\hat{\theta} - \theta)^2$$

UMVUE

- Sensible way of choosing which unbiased estimator to use is to find the unbiased estimator with the smallest possible variance
  - Equivalently, this results in an unbiased estimator with the smallest possible MSE
- Such an estimator is called the *uniformly minimum variance unbiased estimator* (UMVUE)
- Use the Lehmann-Scheffé theorem:
  - Suppose S is a minimal sufficient and complete statistic, and U is an unbiased estimator
  - Then the estimator $\hat{U} = E(U|S)$ is the (unique) UMVUE

UMVCUE

- Consider a multi-arm trial which incorporates *treatment selection*
  - e.g. Treatments are ranked according to some rule and the best treatment(s) are taken forward to the next stage
- In this setting, it is more appropriate to additionally *condition* on the selection used
- This gives the *uniformly minimum variance conditionally unbiased estimator* (UMVCUE)
- Note that the UMVCUE is unbiased unconditionally as well

Median unbiased estimator

- So far, have been considering *mean* unbiasedness (the usual unbiased property)
- A reasonable alternative is to consider *median* unbiasedness
- An estimator θ_{MU} is median unbiased if $Pr(\theta_{MU} \leq \theta) = Pr(\theta_{MU} \geq \theta)$
  - i.e. the estimator underestimates just as often as it overestimates
- Median-unbiased estimators may be easier to construct than mean-unbiased estimators
- Median-unbiased estimators are invariant under one-to-one transformations (unlike mean-unbiased estimators)

Unbiased vs bias-reduced estimators

Why not always use an unbiased estimator?

1. Not (yet) available for all classes of adaptive designs
2. Increased MSE (bias-variance trade-off) leading to large SEs and wide CIs

Bias-adjusted MLE

- Whitehead (1986) proposed a bias-adjusted MLE, which adjusts the MLE $\hat{\theta}_{\text{MLE}}$ to remove bias
- Bias for the MLE as a function of the unknown parameter of interest θ is $b(\theta) = E(\hat{\theta}_{\text{MLE}}|\theta) - \theta$
- Bias-adjusted MLE $\hat{\theta}_{\text{BC}}$ is the numerical solution to

$$\hat{\theta}_{\text{BC}} = \hat{\theta}_{\text{MLE}} - b(\hat{\theta}_{\text{BC}})$$

Review of point estimation for adaptive trials

Received: 25 June 2021 | Revised: 21 October 2022 | Accepted: 1 November 2022
DOI: 10.1002/sim.9605

RESEARCH ARTICLE

Statistics in Medicine WILEY

Point estimation for adaptive trial designs I: A methodological review

David S. Robertson[1] | Babak Choodari-Oskooei[2] | Munya Dimairo[3] | Laura Flight[3] | Philip Pallmann[4] | Thomas Jaki[1,5]

Received: 25 June 2021 | Revised: 20 January 2023 | Accepted: 18 March 2023
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RESEARCH ARTICLE

Statistics in Medicine WILEY

Point estimation for adaptive trial designs II: Practical considerations and guidance

David S. Robertson[1] | Babak Choodari-Oskooei[2] | Munya Dimairo[3] | Laura Flight[3] | Philip Pallmann[4] | Thomas Jaki[1,5]

- Provides a comprehensive overview of proposed approaches for different classes of adaptive designs, with available software
- Illustrates the computation of different estimators in practice using a real trial example
- Proposes a set of guidelines for researchers around the choice of estimators and the reporting of estimates following an adaptive design

Case study

- Two-arm RCT of oral cannabis extract vs placebo in adults with MS
- Primary endpoint: relief from muscle stiffness (yes/no) after 12 weeks
- Two-stage group-sequential design (maximum $n = 300$) with interim analysis (after $n = 200$)
  - O'Brien-Fleming efficacy stopping boundaries
  - Trial continued to the final analysis

	Interim data		Final data	
	Placebo	**CE arm**	**Placebo**	**CE arm**
Number of subjects with relief from muscle stiffness	12	27	21	42
Total number of subjects	97	101	134	143
Standardized test statistic	2.540		2.718	
OBF boundary	2.797		1.977	

Case study

Type of estimator	Estimator	Estimate (SE)	Relative difference
Standard/naive	MLE	0.137 (0.054)	–
Unconditional	MUE	0.134 (0.054)	−2%
	UMVUE	0.1278 (0.054)	−7%
	Bias-corrected MLE	0.133 (0.055)	−3%
Conditional	MUE	0.185 (0.080)	+35%
	UMVCUE	0.172 (0.071)	+26%
	Bias-corrected MLE	0.191 (0.073)	+39%

MLE = Maximum Likelihood Estimator; MUE = Median Unbiased Estimator; UMVUE = Uniform Minimum Variance Unbiased Estimator; UMVCUE = Uniform Minimum Variance Conditionally Unbiased Estimator

Desirable criteria for CIs

1. Correct coverage probability [Essential!]
2. Narrower CIs are to be preferred
3. Consistent/compatible with the hypothesis test
4. Contains the point estimate of interest
5. Is an interval (i.e. not disjoint or the empty set)
6. Computational feasibility/simplicity

Classes of CIs

- Repeated CIs: can be calculated at any stage, not tied to a pre-specified stopping rule, but generally conservative (i.e. wide) and may not always contain the MLE
- Exact/monotone CIs: can only be calculated at the stage a trial stops according to a pre-specified stopping rule, narrower than repeated CIs
- Simultaneous CIs: ‘multiplicity-adjusted’ individual CIs

Methods to construct adjusted CIs

- Constructing an approximate pivotal quantity, e.g. using asymptotic normality
- Inverting a test statistic, i.e. exploiting the duality between confidence set and hypothesis test
- Bootstrap/resampling techniques
- Hybrid approaches, e.g. using different methods for lower and upper confidence bound

Exact confidence intervals

1. Define an ordering of design space w.r.t evidence against $H_0 : \theta = 0$

2. Define a *p*-value function $P(\theta)$: gives probability that, at the stage the trial stopped, even more extreme evidence against H_0 could have been observed

3. At the point the trial stops, a $100 \times (1 - \alpha)\%$ confidence interval for θ is given by $(\hat{\theta}_{lb}, \hat{\theta}_{ub})$ where:

$$P(\hat{\theta}_{lb}) = \frac{\alpha}{2} \quad \text{and} \quad P(\hat{\theta}_{ub}) = 1 - \frac{\alpha}{2}$$

Ordering the design space

- Stage-wise ordering most common
- For two test statistics (z_j, z_k), $P_{z_j}(\theta) \leq P_{z_k}(\theta)$ if:
  - $j < k$ and $z_j \geq e_j$
  - or if $j = k$ and $z_j \geq z_k$
  - or if $j > k$ and $z_k \leq f_k$

Example: Group sequential designs

Repeated confidence intervals

- Proposed by Jennison and Turnbull, 1989
- The RCIs for a parameter θ of interest are a sequence of confidence intervals C_j, $j = 1 \ldots, k$ where

$$P(\theta \in C_j \text{ for stages } j = 1, \ldots, k) \geq 1 - \alpha$$

  for all θ

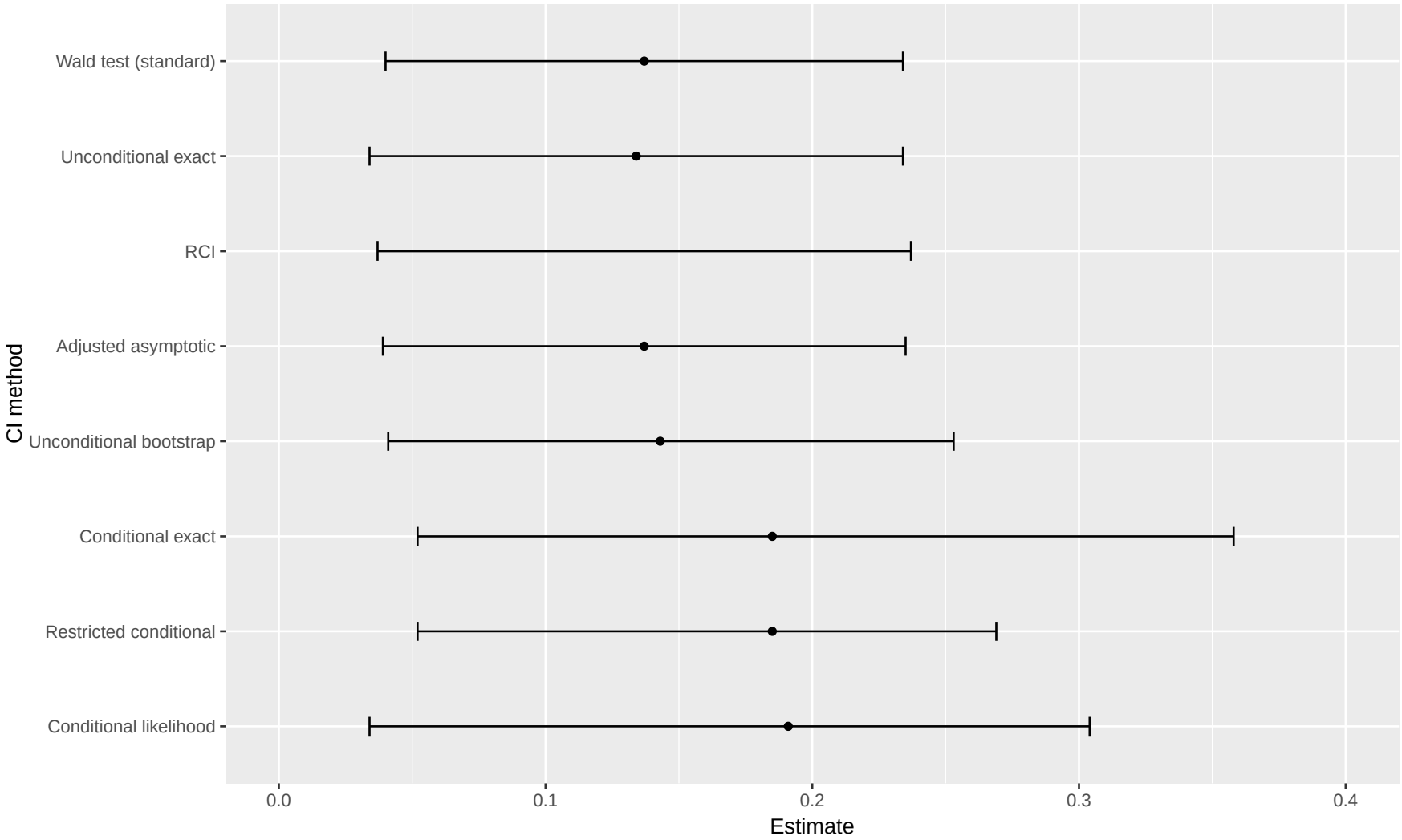
- Can be computed at any stage, whether the trial stops or not, i.e. is valid regardless of how the decision to stop the study was reached

Case study (continued)

Type of CI	CI method	Point estimate	95% CI	CI width
Standard/naive	Wald test	0.137 (MLE)	(0.040, 0.234)	0.194
Unconditional	Exact	0.134 (MUE)	(0.034, 0.234)	0.200
	Repeated	–	(0.037, 0.237)	0.199
	Adj. asymptotic	0.137	(0.039, 0.235)	0.196
	Bootstrap	0.143	(0.041, 0.253)	0.212
Conditional	Exact	0.185 (MUE)	(0.052, 0.358)	0.306
	Restricted Exact	0.185 (MUE)	(0.052, 0.269)	0.217
	Likelihood	0.191	(0.034, 0.304)	0.271

CI = Confidence Interval, MLE = Maximum Likelihood Estimator; MUE = Median Unbiased Estimator; RCI = Repeated Confidence Interval

Case study (continued)



Proposed guidance

- The issue of estimation should be considered throughout the whole lifecycle of an adaptive trial
- The design and analysis of an adaptive trial are closely linked, and one should not be considered without the other
- Our main focus is on the confirmatory setting where analyses are fully pre-specified
- Builds on the relevant parts of the FDA and EMA guidance for adaptive designs and the adaptive designs CONSORT extension

Proposed guidance

Planning stage

- Decide on what exactly is to be estimated (i.e. the estimands of interest)
- Decide on the desired characteristics of estimator:
  - Conditional versus unconditional perspective (see Marschner 2021)
  - Bias-variance trade-off for point estimators
  - Trade-off in metrics for CIs
  - Link between CIs and point estimators
- A review of the literature may be sufficient
- Otherwise, conduct simulations to explore

Proposed guidance

Pre-specification of analyses

- Statistical analysis plan (SAP) and health economic analysis plan (HEAP) should include a description and justification of the estimators and CIs used
- When available, unbiased or bias-reduced estimators should be used and reported alongside the standard MLE
- If multiple adjusted estimators/CIs are available and are of interest, one adjusted estimator/CI should be designated the 'primary' adjusted estimator/CI
  - Others included as sensitivity or supplementary analyses

Proposed guidance

Reporting results for a completed trial

- There should be a clear description of the statistical methods used to estimate treatment effects
- Adjusted estimates taking the trial design into account are to be preferred
- FDA guidance: *"if naive estimates such as unadjusted sample means are used, the extent of bias should be evaluated, and estimates should be presented with appropriate cautions regarding their interpretation"*
- EMA guidance: *"methods to . . . provide confidence intervals with pre-specified coverage probability are required"*

Final thoughts

- Point estimates and CIs need adjusting after an adaptive design
- There is a growing body of methodological literature proposing point estimators and CIs for a variety of adaptive trial designs
- However, there has been relatively little uptake of adjusted point estimators (and CIs) in practice
- Need for the further development of user-friendly software and code
- Preprints of CI work coming soon (two papers)

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