Implementing ICH E20:

Designing and Analysing Adaptive Clinical Trials

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Plan of the workshop

Introduction to ICH E20, key principles, scope of E20

Group discussion and reporting

Overview of adaptive methods

Group discussion and reporting

Conclusions

The International Council for Harmonisation (ICH)

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Founded in 1990, originally formed of members from Europe, Japan and the US

Brings together regulatory authorities and the pharmaceutical industry to discuss and establish scientific and technical guidelines for drug registration

Seeks to **standardise regulatory requirements** for pharmaceutical products **worldwide**

The ICH E20 process

A new topic is proposed by an ICH Member or Observer for approval by the ICH Assembly

An Informal Working Group is then formed to create a Concept Paper, offering additional context and outlining objectives

An Expert Working Group (EWG) is established to develop a comprehensive plan

For ICH E20, Concept Paper and EWG formed in Nov 2019

The Draft document was signed off in June 2025 to be issued by the ICH Regulatory Members for public consultation

Focus is on confirmatory trials with an adaptive design

The ICH E20 Expert Working Group

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ICH Assembly Meeting, Singapore, Nov 17-20, 2019

Definitions of adaptive design

PhRMA ADWG (2006): Adaptive Design is one that uses accumulating data from the ongoing trial to modify aspects of the study without undermining the validity and integrity of the trial

EMA Reflection Paper (2007): A study design is adaptive if statistical methodology allows the modification of a design element (e.g. sample-size, randomization ratio, number of treatment arms) at an IA with full control of the type I error

Draft NPMA (2019): A clinical trial design that will have adaptations based on the accumulating data from the trial and/or external data. Modifications based on the accumulating data from the trial should be pre-specified prior to initiation of the trial

FDA Guidance on AD (2019): Adaptive design is defined as a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial

ICH E20 (2025): *An adaptive design is defined as a clinical trial design that allows for prospectively planned modifications to one or more aspects of the trial based on interim analysis of accumulating data from participants in the trial*

ICH E20: Scope

Guidance on confirmatory clinical trials with an adaptive design intended to evaluate a treatment for a given medical condition within the context of its overall development program

Out of scope:

- Trials with unplanned modifications to the design
- Design changes based entirely on emerging information from a source external to the trial
- Routine monitoring of operational aspects

Focus on principles for the planning, conduct, analysis, and interpretation of trials with an adaptive design intended to confirm the efficacy and support the benefit-risk assessment of a treatment

ICH E20: Advantages and Challenges of Adaptive Designs

Advantages:

- Ethical advantages, reducing participants subjected to less effective treatments
- Improved trial efficiency by boosting statistical power
- Enhanced comprehension of treatment outcomes and support for informed decisions

Challenges:

- Logistical complexities and heightened risk to trial integrity
- Early termination may introduce bias in effect estimates
- May not always be appropriate, e.g. with rapid enrollment
- Essential to provide comprehensive justification and assessment

ICH E20: The 5 Key Principles

Adequacy within development program Justify selected dose, etc.

Adequacy of trial planning Pre-planned, as simple as possible

Limiting the chances of erroneous conclusions Type I error control

Reliability of estimation Estimates and CIs for cost-benefit decisions

Maintenance of trial integrity Blinding, avoiding information leakage, role of IDMCs

"All of these principles should be followed regardless of the type of adaptation and statistical approach (e.g., frequentist or Bayesian methods)."

Types of Adaptation

Early Trial Stopping

Sequential analyses to stop trials early for efficacy/futility, with type I error control

Early stopping may limit safety data and secondary endpoint information

Sample Size Adaptation

Adjusts initial sample size based on interim estimates to ensure adequate power

Requires pre-specified rules, use of blinded data, and methods to control type I error

Population Selection

Enables focus on specific subpopulations to improve trial efficiency and relevance

Needs thorough planning, justification, and statistical methods to control type I error

Treatment Selection

Uses interim data to select the most promising treatment doses/options

Requires detailed planning, pre-specified rules, and methods to control type I error

Adaptation to Participant Allocation

Assigns more participants to better-performing treatments

Challenges include bias, confounding from time trends, and ensuring valid inference

Special topic 1: Data monitoring

- "*...further considerations for adaptive designs with unblinded interim analysis of accumulating data*"
- The expert IDMC (including a statistician and **all expertise** needed to make adaptation recommendations) must operate under a detailed charter and ensure alignment with the sponsor on all adaptive rules, in addition to core safety role.
- An external, independent group with necessary expertise must be established to conduct unblinded analyses, holding sole access to interim data for the IDMC. Adaptations must be **implementable by the sponsor without unblinded data** access.
- Any proposed access by sponsor to unblinded data requires compelling rationale, rigorous integrity measures (firewalls), detailed documentation for regulatory review.

Special topic 2: Conducting & reporting simulation studies

- *"..simulations play an important role planning an adaptive design and for understanding their operating characteristics"*
- Simulation scenarios must cover the **plausible range of assumptions** (treatment effects, nuisance parameters, and operational factors like recruitment rates and dropout rates)
- Include a **benchmark** design to quantify trade-offs and inform the final choice.
- Pre-define and assess a broad set of operating characteristics and evaluate the variability/distribution of results
- Emphasis on reproducibility and explicit links between clinical assumptions and statistical results

Special topic 3: Adaptive designs using Bayesian methods

- *"This section is not fully harmonized"*
- Bayesian methods are considered when clearly justified and resulting conclusions are sufficiently robust (as per ICH E9).
- Expectations for operating characteristics are the same as for non-Bayesian adaptive designs
  - Set all elements (prior distribution, decision criteria, and adaptation rules) to achieve targets while **controlling the Type I error rate**.
- Special case: adaptive designs with borrowing of external information via an informative prior
  - Must address the feasibility of running a fully powered trial without borrowing and support the relevance & quality of the external data used
  - Concern around misspecification of the informative prior

Special topic 4: Adaptive designs in time-to-event settings

- In time-to-event trials, the focus is on the number of events, often leading to interim analyses based on number of events, with possible adjustments to the number of events or follow-up time.
- Adaptive designs should ensure sufficient data for benefit-risk assessments, especially when increasing the number of participants or follow-up duration to observe more events.
- Maintaining independence between data collected before and after interim analyses is crucial; using participant data that contribute to both stages can inflate Type I error.
- Strategies to control error include pre-specified adaptation rules based only on the primary endpoint, defining participant sets for each stage, or early stopping based on event counts.
- Similar considerations apply to longitudinal outcomes.

Special topic 5: Adaptive designs in exploratory trials

- The guideline emphasizes applying key principles to adaptive designs in confirmatory trials to ensure reliable evidence for benefit-risk assessment
- Adaptive designs can also be used early in development for dose, regimen, population, or endpoint decisions, but principles still apply to maintain interpretability
- Exploratory trials may allow general adaptation principles rather than strict rules, but they must still provide a solid basis for subsequent confirmatory phases
- Sponsors should balance involvement in interim decisions with maintaining trial integrity, ensuring participant safety and minimizing bias

Special topic 6: Operational considerations

- Operational challenges, such as maintaining trial integrity, should be addressed during trial planning, including measures to limit inference from interim analyses.
- Informed consent forms must explain the possibility of adaptive changes, their purpose, and the continued protection of participants' rights and safety.
- Data management systems should be capable of handling scenario changes with minimal sponsor involvement
- Drug supply logistics can be strained by rapid adaptations, especially across multiple countries, necessitating careful planning and simulation to support supply chain decisions.
- Processes for timely data validation and cleaning, including formal interim database locks, are essential to ensure high-quality data for adaptation decisions

Breakout groups

Questions:

Which types of adaptive trial design have you implemented or analysed?

Did your trials meet the E20 requirements?

If not, how might you have modified your trials to meet the new requirements?

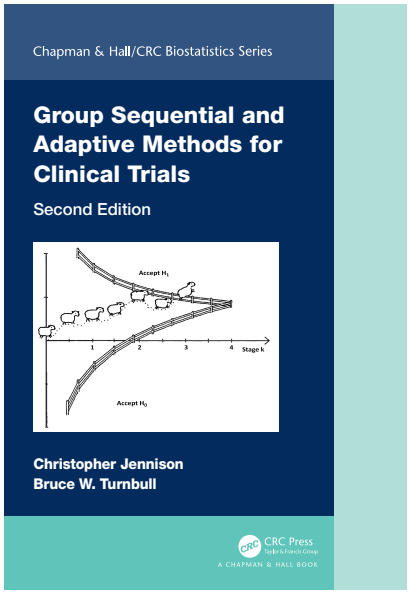
Types of adaptive design, methods and challenges

Many research papers and several books describe methods that can meet some of the ICH E20 guidelines.

See, for example,

Group Sequential and Adaptive Methods for Clinical Trials,

Jennison & Turnbull, 2026.



Existing methods may have to be applied in particular ways to satisfy the E20 principles.

Some methods may need further development to satisfy E20 principles.

1. Group sequential tests

Objective

Facilitate early stopping for efficacy or futility

Methods

To protect the type I error rate: *Error spending tests*

Computations for inference on termination

One-sided error spending tests

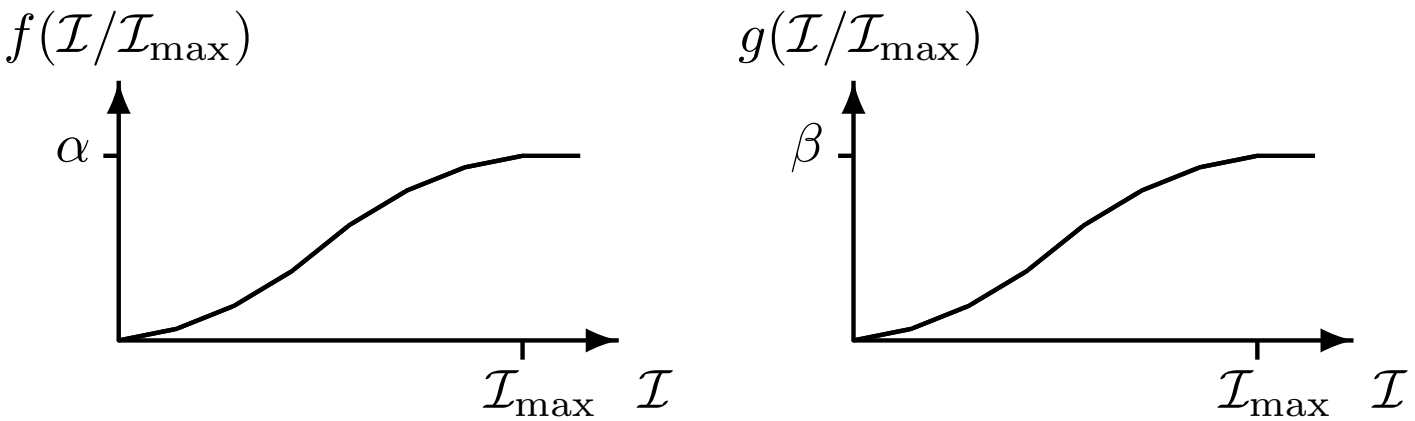
For treatment effect θ, we test H_0: $\theta \leq 0$ against $\theta > 0$ with

Type I error probability α at $\theta = 0$

Type II error probability β at $\theta = \delta$

Let $\mathcal{I}_k = \{\text{Var}(\widehat{\theta}_k)\}^{-1}$ where $\widehat{\theta}_k$ is the estimate of θ at analysis k.

We specify two error spending functions



Type I error probability α is spent according to the function $f(\mathcal{I}/\mathcal{I}_{\max})$, and type II error probability β according to $g(\mathcal{I}/\mathcal{I}_{\max})$

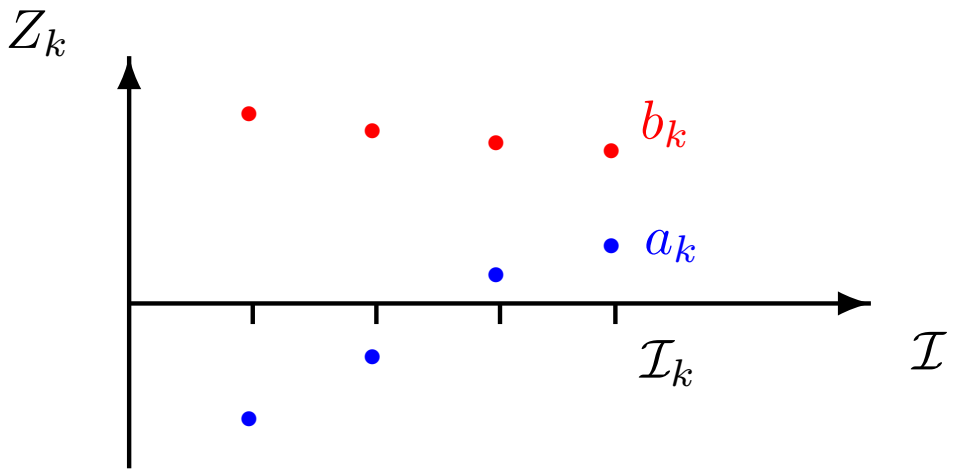
One-sided error spending tests

Analysis k: With observed information $\mathcal{I}_k$, we find a_k and b_k to satisfy

$$P_{\theta=0}\{a_1 < Z_1 < b_1, \ldots, a_{k-1} < Z_{k-1} < b_{k-1}, Z_k > b_k\}$$
$$= f(\mathcal{I}_k/\mathcal{I}_{\max}) - f(\mathcal{I}_{k-1}/\mathcal{I}_{\max})$$

and

$$P_{\theta=\delta}\{a_1 < Z_1 < b_1, \ldots, a_{k-1} < Z_{k-1} < b_{k-1}, Z_k < a_k\}$$
$$= g(\mathcal{I}_k/\mathcal{I}_{\max}) - g(\mathcal{I}_{k-1}/\mathcal{I}_{\max})$$



Group sequential tests

Challenges

Early stopping for efficacy should only happen when there is:

- Adequate safety data
- The information needed to make cost-benefit decisions

Avoiding bias in estimates of treatment effects

2. Sample size adaptation

Objective

Respond to interim estimates of:

- Nuisance parameters
- The treatment effect on the primary endpoint

Methods

- **Combination tests**
  - "Conditional probability of rejection" principle

Combination tests

Before the trial commences, define the null hypothesis

Let θ denote the treatment effect *vs* control for a specified form of the treatment, patient population and endpoint

Suppose we wish to test H_0: $\theta \leq 0$ against $\theta > 0$, with type I error rate α at $\theta = 0$ when sample size may be re-assessed after Stage 1

Define one-sided P-values $P^{(1)}$ and $P^{(2)}$ from hypothesis tests of H_0 based on Stage 1 and Stage 2 data, respectively

Then, under $\theta = 0$

$P^{(1)} \sim U(0,1)$

Conditionally on Stage 1 data and the Stage 2 design (informed by Stage 1 data), $P^{(2)} \sim U(0,1)$

Hence, if $\theta = 0$, $P^{(1)}$ and $P^{(2)}$ are independent $U(0,1)$ variates

The inverse normal combination test

Initial design

Specify the **inverse normal test** for null hypothesis H_0, with weights w_1 and w_2 where $w_1^2 + w_2^2 = 1$

Design Stage 1, fixing sample size and test statistic

Stage 1

Observe the one-sided P-value, $P^{(1)}$, based on Stage 1 data

Compute $Z^{(1)} = \Phi^{-1}(1 - P^{(1)})$

Design Stage 2 in the light of Stage 1 data

Stage 2

Observe the P-value, $P^{(2)}$, based **only** on Stage 2 data

Compute $Z^{(2)} = \Phi^{-1}(1 - P^{(2)})$

The inverse normal combination test

Under $\theta = 0$

We know $P^{(1)} \sim U(0,1)$ and $P^{(2)} \sim U(0,1)$ are independent

Hence $Z^{(1)} \sim N(0,1)$ and $Z^{(2)} \sim N(0,1)$ are independent and

$$w_1 Z^{(1)} + w_2 Z^{(2)} \sim N(0,1)$$

For a one-sided test with type I error rate α, we reject H_0 if

$$w_1 Z^{(1)} + w_2 Z^{(2)} > \Phi^{-1}(1-\alpha)$$

If $\theta < 0$, then $Z^{(1)}$ and $Z^{(2)}$ are stochastically smaller than $N(0,1)$ random variables and the type I error rate is less than α

Here, it is crucial that w_1 and w_2 are pre-specified and not changed in response to observed data

Example: Phase 3 Schizophrenia trial

See Mehta and Pocock (2010) for more details

Test vs active comparator, based on improvement from baseline to week 26 in Negative Symptoms Assessment (a standardized score)

Initial design is powered for difference of $\theta = 2$, where θ is mean difference in change from baseline in NSA. But a difference of $\theta = 1.6$ would still be clinically meaningful

~ 440 patients needed for $\theta = 2$, but ~ 690 needed for $\theta = 1.6$, assuming 80% power requirements at $\alpha = 0.025$ one-sided

A group-sequential design option conducts final analysis at ~ 690 patients

Interim analysis based on when ~ 200 patients have data, using O'Brien-Fleming like bound

Example: Phase 3 Schizophrenia trial

A trial with the sample size adaptation option plans for ~ 440 patients

At the interim analysis after ~ 200 patient responses are observed, decide whether to go up to a sample size of potentially 884 patients

It is important to compare designs' operating characteristics. The adaptive option provides power gain, but at cost of increased expected sample size: see Jennison & Turnbull (2015)

For either approach, methodology exists to adjust point estimates

The adaptive option has the issue of sample size being linked to the interim effect estimate, so knowledge of the revised sample size means you have (some) knowledge of the interim effect

Sample size adaptation

Challenges

Trial integrity: blinding, information leakage

Avoiding bias in estimates of treatment effects

3. Population selection

Objective

Focus on the sub-population in which a new treatment is most effective, "enriching" the sample size in that sub-population

Methods

Combination tests and a **closed testing procedure** (CTP) to control the family-wise error rate (FWER)

An effective (possibly Bayes) rule to decide when to enrich

Testing multiple hypotheses: the family-wise error rate

In an enrichment trial, we may test for a treatment effect in the full population and various sub-populations.

Adaptations are to drop certain sub-populations and concentrate on subjects with the best response to the new treatment.

In analysing the data, we wish to control the overall probability of a false positive conclusion.

The family-wise error rate

Suppose we have h null hypotheses, H_i: $\theta_i \leq 0$ for $i = 1, \ldots, h$.

A procedure's **family-wise error rate** when $\boldsymbol{\theta} = (\theta_1, \ldots, \theta_h)$ is

$$P_{\boldsymbol{\theta}}\{\text{Reject } H_i \text{ for some } i \text{ with } \theta_i \leq 0\}.$$

The family-wise error rate is controlled **strongly** at level α if this error rate is at most α for all possible combinations of θ_i values, so

$$P_{\boldsymbol{\theta}}\{\text{Reject any true } H_i\} \leq \alpha \quad \text{for all } \boldsymbol{\theta} = (\theta_1, \ldots, \theta_h).$$

Controlling family-wise error: closed testing procedures

Marcus et al. (*Biometrika*, 1976) introduced a **closed testing procedure** which provides strong control of FWER by combining level α tests of each H_i and of intersections of these hypotheses.

Suppose we have null hypotheses H_i, $i = 1, \ldots, h$.

For each subset I of $\{1, \ldots, h\}$, define the intersection hypothesis

$$H_I = \cap_{i \in I} H_i.$$

— a simple hypothesis H_j is a special case where $I = \{j\}$.

Construct a level α test of each intersection hypothesis H_I, i.e., a test which rejects H_I with probability at most α whenever all hypotheses specified in H_I are true.

Closed testing procedure

The simple hypothesis H_j: $\theta_j \leq 0$ is rejected overall if, and only if, H_I is rejected for every set I containing index j.

Using combination tests and a closed testing procedure

Suppose an enrichment trial is conducted in two stages and adaptation may occur at the end of Stage 1.

Initially, there are h populations or sub-populations for which a null hypothesis of no treatment effect may be tested.

We need to define a level α test for each intersection hypothesis

$$H_I = \cap_{i \in I} H_i$$

In a two-stage adaptive trial, each stage provides a P-value for H_I, $P_I^{(1)}$ in Stage 1 and $P_I^{(2)}$ in Stage 2.

The way in which the $P_I^{(1)}$ are to be calculated is specified at the start of the trial and the way in which the $P_I^{(2)}$ are to be calculated must be stated before commencing Stage 2.

We combine these P-values across stages by a pre-specified method, e.g., an inverse normal combination test.

Example: TAPPAS trial

- TAPPAS was a trial of TRC105 (an antibody) and pazopanib vs pazopanib alone in patients with advanced angiosarcoma
- Two subgroups: cutaneous and non-cutaneous advanced angiosarcoma
- Primary endpoint = PFS, initial sample size of 124 patients to be followed until 95 events (progression or death) observed
- Enrichment design with 3 possibilities at interim analysis:
  - Continue as planned with the full population
  - Continue with full population and increase sample size (recruiting 200 patients followed until 170 events in total)
  - Continue with only the cutaneous subgroup (recruiting 170 patients followed until 110 events in total)
- The study recruited from the full population throughout and concluded that TRC105 did not demonstrate activity when combined with pazopanib

Population selection

Challenges

- Justifying the choice of sub-population
- Adequate information on (lack of) treatment efficacy in the complementary population
- Avoiding bias in estimates of treatment effects

4. Seamless Phase 2/3 and Multi-arm Multi-stage trials

Objectives

Seamless Phase 2/3: Use Phase 2 data at interim analysis to choose a treatment/dose to take to the Phase 3 stage, then test for a difference between the selected treatment/dose and control (using Phase 2 and Phase 3 data)

Multi-arm Multi-stage (MAMS): simultaneous comparison of multiple experimental treatments/doses (with a common control). Use interim data to focus on the most promising treatments/doses

Methods

Pool information across stages with combination tests and a closed testing procedure (with Dunnett tests) to control FWER

Types of adaptive design, methods and challenges

Treatment selection and multi-treatment trials

Challenges: Seamless Phase 2/3 trials

- Operational aspects of combining phases of testing a new drug
  - Decision making with IDMC
  - Pre-specifying details of the Phase 3 stage
- Avoiding bias in estimates of treatment effects

Challenges: Multi-arm Multi-stage trials

- Operational aspects: standardisation and randomisation, upfront set-up costs
- Avoiding bias in estimates of treatment effects

5. Response-adaptive randomisation (RAR)

Objective

Most common: use interim data to identify better-performing treatments and allocate more patients to these treatments

Methods

- Simulation-based tests
- Randomisation-based tests
- Exact tests for binary outcomes

Example: ARREST trial

- Advanced REperfusion STrategies for Refractory Cardiac (ARREST) trial compared **ECMO** vs standard advanced cardiac life support resuscitation (**ACLS**)
- The PIs wanted to use RAR to minimise patient exposure to the inferior treatment
- Bayesian RAR used with possibility of early stopping for efficacy or futility
- Randomisation probabilities updated every 30 patients using posterior probability that ECMO response rate $>$ ACLS response rate, truncated to lie within (0.25, 0.75)
- The first group of patients acts as a **burn-in** of size 30 with equal allocation probability for each arm
- Simulation-based inference to control type I error rate
- The trial stopped at the first interim analysis for efficacy

Types of adaptive design, methods and challenges

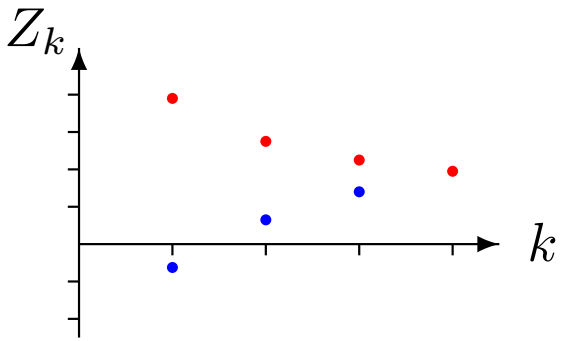
Challenges: Response-adaptive randomisation

Confounding from time trends

Maintaining uncertainty in treatment allocation

Valid statistical inference on completion of the trial

All types of adaptation: Estimation after an adaptive trial



In a group sequential trial comparing two treatments, the maximum likelihood estimate (MLE) of θ when the trial stops at analysis k is

$$\widehat{\theta}_M = \bar{X}_{Ak} - \bar{X}_{Bk}.$$

For large, positive values of θ:

high values of $\widehat{\theta}$ lead to early stopping,

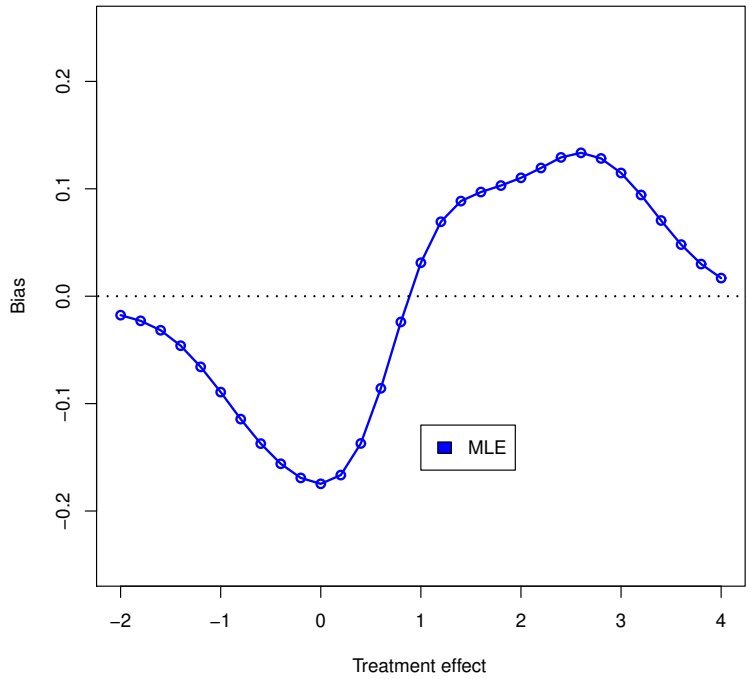
lower values of $\widehat{\theta}$ result in more observations, so $\widehat{\theta}$ can increase.

Thus, the MLE is biased with $E_\theta(\widehat{\theta}_M) > \theta$ for high values of θ and $E_\theta(\widehat{\theta}_M) < \theta$ for low values of θ.

Bias of the MLE of θ after a Pampallona & Tsiatis test

Consider a Pampallona & Tsiatis group sequential design with 4 analyses, $\Delta = 0$, $\alpha = 0.025$ and power $1 - \beta = 0.8$ at $\theta = 1$

The bias of the MLE can be calculated as a function of the true effect size, θ.



The bias of the MLE is around 0.1 at values of θ just above 1.

Correcting the bias of the MLE

Denote the bias function of the MLE by

$$b(\theta) = E_\theta(\widehat{\theta}_M) - \theta.$$

Whitehead (*Biometrika*, 1986) suggested correcting the MLE by subtracting an estimate of its bias.

Although the true θ is unknown, the bias of the MLE can be estimated by $b(\widehat{\theta}_M)$.

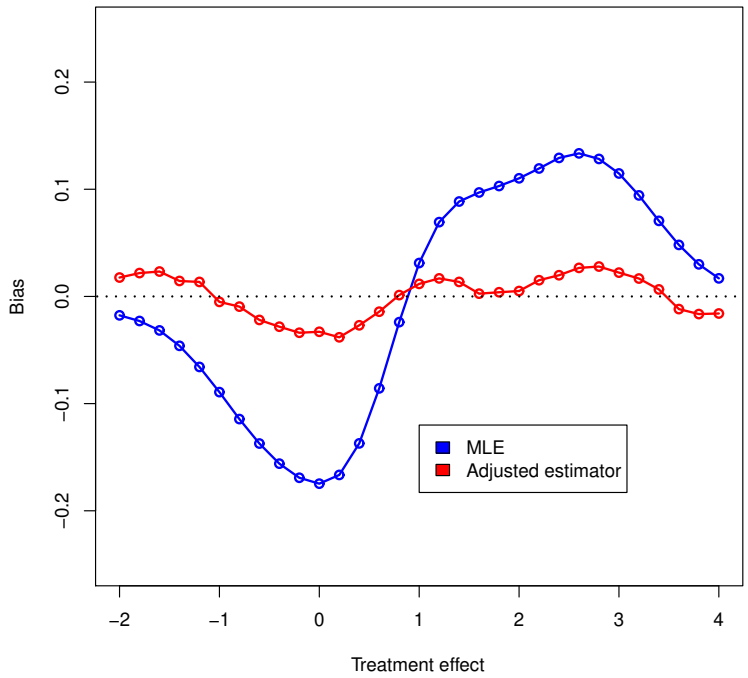
The adjusted estimator is then

$$\widehat{\theta}_{adj} = \widehat{\theta}_M - b(\widehat{\theta}_M).$$

Bias of the MLE of θ after a Pampallona & Tsiatis test

Simulation results show that Whitehead's adjusted estimator has much smaller bias than the MLE on which it is based.

For our example:



The adjustment almost completely removes the bias in the MLE.

Unbiased estimation after a group sequential test

ICH E20:

Key principle number 4 concerns "Reliability of estimation".

It is noted that, while controlling the chances of false positive efficacy conclusions is expected,

> *In addition, reliable estimation of treatment effects for the primary efficacy endpoint and other key efficacy and safety outcomes is important.*
>
> *In the trade-off between bias and variance, the expectation is generally for* **limited to no bias** *in the primary estimate of the treatment effect.*

It may be surprising to suppose it is possible to give an estimate with "no bias" after a group sequential or adaptive trial.

Unbiased estimation after a group sequential test

Emerson & Fleming (*Biometrika*, 1990) showed that an unbiased estimate can be obtained after a group sequential test.

The MLE based on the data at analysis 1, $\widehat{\theta}_1$, is unbiased for θ. and one can apply "Rao-Blackwellization", calculating the conditional expectation of $\widehat{\theta}_1$ given the final set of data to obtain an unbiased estimate of θ.

The numerical methods used to compute properties of a group sequential test can be adapted to compute this Uniform Minimum Variance Unbiased Estimate (UMVUE)

However, an unbiased estimator may have a large variance and a relatively high mean square error.

The UMVUE may also be rather strange: it can reduce the MLE by an amount that is much higher than the bias of the MLE under any θ value.

Unbiased estimation after an adaptive design

In more complex adaptive designs, bias may arise

(i) from selecting a treatment arm or patient sub-population based on promising early results,

(ii) from early stopping on a "random high".

Some of the methods proposed for estimation after such trials also use Rao-Blackwellization to find UMVUE or Uniform Minimum Variance Conditionally Unbiased Estimates.

Given the behaviour of the UMVUE estimate seen in examples of group sequential tests of a single hypothesis, with a single parameter to estimate, we should look more closely at how these estimates may behave.

Adjusted estimates with a small bias may well be preferable.

The independent data monitoring committee (IDMC)

Some reflections of experience on IDMCs ...

Suggestions for sponsors

- Imagine you are an IDMC member
- Consider the expertise you need as the IDMC statistician
- After the kick off meeting, a firewall will be in place: what questions would you want to ask at this meeting?
- List the "what if" scenarios you would want to discuss

Remember: A typical company statistician may not have experience as an IDMC member.

Maintaining independence properties of p-values based on data from before and after interim analyses

Example: A study in oncology with treatment selection (GATSBY)

Experimental Treatment 1: Intensive dosing

Experimental Treatment 2: More frequent lower doses

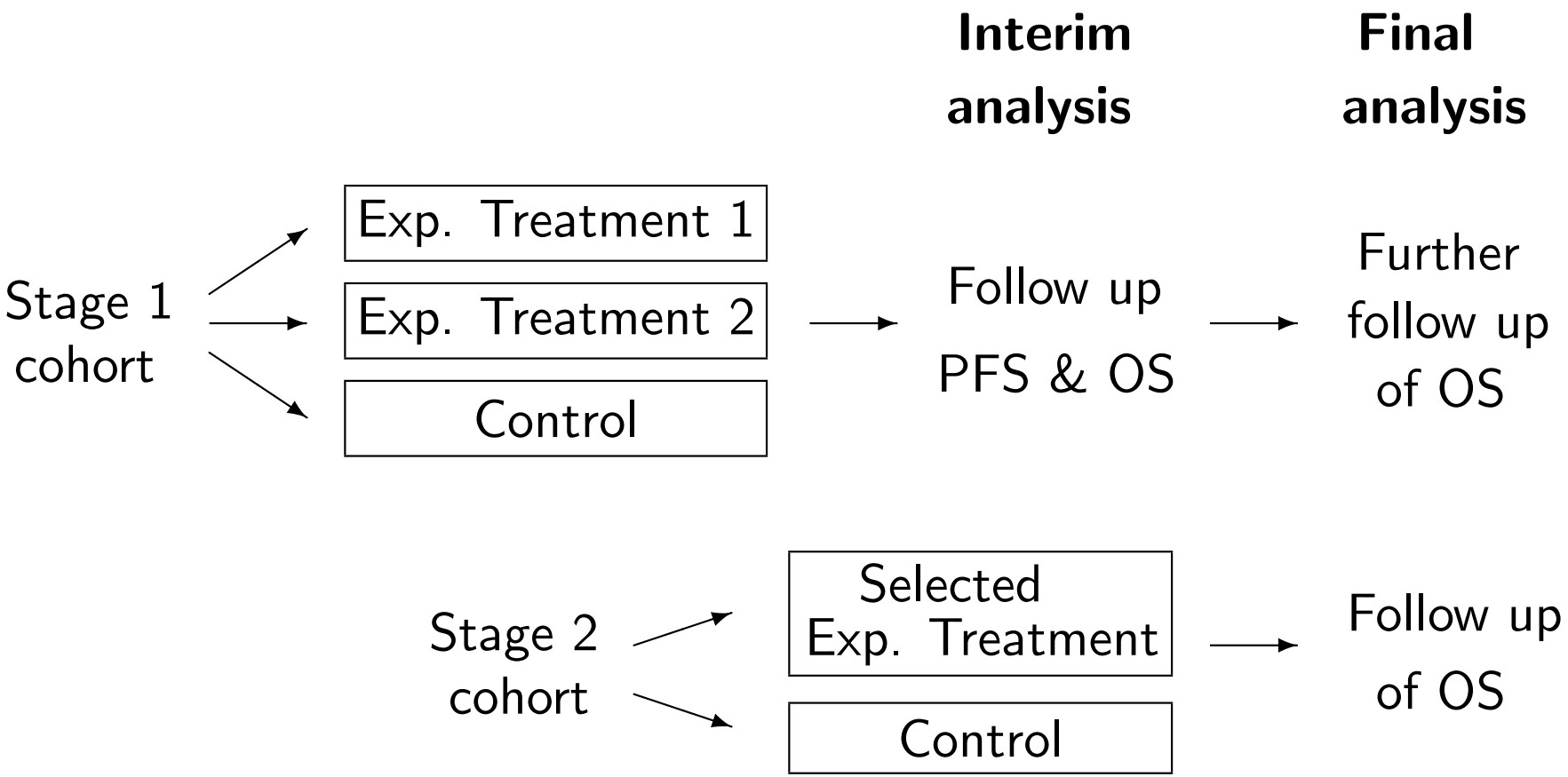
Control treatment

The primary endpoint is Overall Survival (OS).

At an interim analysis, information on OS, Progression Free Survival (PFS), PK measurements and safety will be used to choose between the two experimental treatments.

After the interim analysis, patients will only be recruited to the selected treatment and the control.

Overall plan of the trial



At the final analysis, we test the null hypothesis that OS on the selected treatment is no better than OS on the control treatment.

Jenkins, Stone & Jennison (*Pharm. Statist.*, 2011)

If we base a combination test on the two parts of the data accrued before and after the interim analysis, bias can result:

	Z_1	Z_2
Stage 1 cohort	Overall survival (during Stage 1)	**Overall survival (during Stage 2)**
Stage 2 cohort		Overall survival (during Stage 2)

Instead, we divide the data into the parts from the two cohorts:

Stage 1 cohort	Overall survival (during Stage 1)	Overall survival (during Stage 2)	Z_1
Stage 2 cohort		Overall survival (during Stage 2)	Z_2

Breakout groups

Questions:

How familiar are you and your colleagues with the adaptive methods needed to satisfy ICH E20?

Do you have the knowledge and software to apply the methods?

Do your IDMCs have the expertise needed to monitor adaptive trials effectively?

Can you identify areas where training would be beneficial?