A framework for the pre-specification of statistical analysis strategies in clinical trials (Pre-SPEC)
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Abstract
Bias can be introduced into clinical trials if statistical methods are chosen based on subjective assessment of the trial data. Pre-specification of the planned analysis approach is essential to help reduce such bias. However, many trials fail to adequately pre-specify their statistical analysis approach, thereby allowing analysts to choose the method which gives the most favourable result. We propose a five-point framework for the pre-specification of the statistical analysis strategy for a clinical trial’s primary outcome (the Pre-SPEC framework); this framework is designed to ensure that methods cannot be chosen based on the trial data in order to give a more favourable result. The five points are: (1) Pre-specify before recruitment to the trial begins; (2) Specify a single primary analysis strategy; (3) Plan all aspects of the analysis; (4) Enough detail should be provided so that a third party could independently perform the analysis; and (5) Adaptive analysis strategies should use deterministic decision rules. This framework could be used as a template to help plan an analysis strategy, or to evaluate whether an existing strategy is at risk of bias due to inadequate pre-specification.
Introduction

Results from clinical trials depend upon the statistical methods used for analysis [1-5]. Different methods of analysis can lead to different conclusions around effectiveness and safety [1-14]. When statistical methods are chosen or altered based on subjective assessment of the trial data, or multiple analyses are performed, then bias can be introduced through selective reporting of results [1-5, 7-10, 12, 15]. Pre-specification of the planned analysis approach is therefore important to prevent and identify subjective data-driven analyses and reporting [1-5, 7, 9, 10, 12]. The ICH-E9 (International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) and SPIRIT (Standard Protocol Items: Recommendations for Intervventional Trials) guidelines require that the method of analysis for the trial’s primary outcome be pre-specified in the trial protocol [1, 3, 4].

However, many trials either fail to fully pre-specify their statistical analysis approach, or do so in a manner which allows subjective data-driven analyses or reporting (table 1) [2-5]. For example, two reviews which examined trial protocols found that 11-20% of protocols did not specify the analysis model that would be used for the primary outcome, 42% did specify the model but omitted essential detail on how the model would be implemented, and 19% specified an approach that would allow the investigators to subjectively choose the final analysis model based on the trial data [2, 5].

In this article, we propose a five point framework for pre-specification of the statistical analysis strategy for a trial’s primary outcome (the Pre-SPEC framework). This framework is designed to ensure that methods cannot be chosen based on the trial data in order to give a more favourable result [2-4], and is consistent with the principles outlined in the SPIRIT and ICH-E9 guidelines [1, 3, 4].

The Pre-SPEC framework

We now outline the Pre-SPEC framework (box 1). The five points are: (1) Pre-specify before recruitment to the trial begins; (2) Specify a single primary analysis strategy; (3) Plan all aspects of the analysis; (4) Enough detail should be provided so that a third party could independently perform the analysis; and (5) Adaptive analysis strategies should use deterministic decision rules. We expand on each of these points below.

*Pre-specify the analysis strategy before recruitment to the trial begins*

Pre-specifying the analysis strategy before the trial begins ensures the choice of methods is not influenced by any trial data. This can give readers confidence that trial results are not due to post-hoc model selection by the investigators [1, 3, 4].

*Specify a single primary analysis strategy*

Specifying a single primary analysis strategy ensures investigators cannot perform multiple analyses and then selectively report the most favourable as their main approach. There are often valid reasons to specify additional methods of analysis, for instance to answer different questions about the intervention (e.g. the effect of a treatment policy vs the effect if everyone adheres [16]), or to assess the robustness of the main results to different assumptions about the data (e.g. sensitivity analyses for missing data [17]); in these instances, a single approach should be clearly labelled as the primary analysis strategy, with other approaches identified as sensitivity or supplementary analyses as appropriate [1, 3, 4].
Plan all aspects of the statistical analysis
Omission of a particular aspect from the analysis strategy could allow investigators to run multiple analyses for that aspect, and selectively report the most favourable. For example, if the analysis population is not specified, investigators could run both an intention-to-treat and per-protocol analysis, and present whichever is most favourable.

Some of the essential aspects to cover are:
- Analysis population
- Statistical model
- The use of covariates
- Handling of missing data

For many trials there will be additional aspects to cover; for instance, a trial using a Bayesian analysis would need to pre-specify what prior would be used for the primary analysis; a non-inferiority trial would need to specify the non-inferiority margin; and a trial where post-randomisation events such as use of rescue medication are likely to occur would need to specify how these events would be handled in the analysis, if relevant.

It is also useful to specify the type of treatment effect that is to be estimated (the estimand) [16] and what information will be presented from the analysis, such as the level of the confidence interval and the threshold for statistical significance if applicable.

Enough detail should be provided so that a third party could independently perform the analysis
There is often a substantial amount of detail required to implement an analysis. For example, using multiple imputation for missing data requires specification of the method of imputing data; this includes specifying which variables are included in the imputation model (and how they are included), whether multivariate normal, chained equations or some other imputation approach is used, the number of imputed datasets, and how imputed datasets will be combined. Simply stating that multiple imputation will be used is not sufficient, as this allows the investigator to carry out multiple analyses based on different imputation approaches.

Fully pre-specifying these details to such a degree that a third party could independently perform the analysis helps to ensure investigators cannot perform multiple analyses. A good test of whether there is sufficient detail is to write out the statistical code that would be used to implement the analysis in a statistical software program; if investigators are unable to write out their planned code, this likely means the analysis strategy is not sufficiently well specified.

In addition, providing this code in the protocol as a supplement to a description of the planned analysis can be extremely helpful, as this leaves no room for ambiguity, and ensures all necessary detail is provided.

Adaptive analysis strategies should use deterministic decision rules
Sometimes investigators use adaptive analysis strategies, where some aspect of the final analysis is chosen based on the trial data. For instance, they may specify that either multiple imputation or a
complete case analysis will be used depending on the level of missing data. However, adaptive analysis
strategies can be problematic if the decision rules are subjective, as this allows investigators to perform
each potential analysis and selectively report the most favourable. For example, without a clear rule
about when to use multiple imputation vs. complete cases, analysts could perform both and then select
whichever gives a preferable result.

In order to prevent decisions from being driven by results, adaptive analysis strategies should use
deterministic decision rules for selection of the final analysis approach. This removes the investigators'
ability to influence decisions, and therefore will not introduce bias through selective reporting. In the
example above, investigators could specify that multiple imputation will be used if the level of missing
data is >10%, and a complete case analysis will be used otherwise.

Sometimes investigators try to reduce the possibility of bias from subjective decision rules through other
means, for instance by using a blinded dataset with treatment allocation codes removed to select the
final analysis approach. We do not favour such approaches, as they generally do not ensure that bias
cannot be introduced through the subjective application of the decision rules. For example, an
investigator using a blinded dataset to select baseline covariates to include in the analysis model could
systematically choose covariates which substantially lowered the residual standard deviation of the
outcome; this could lead to an underestimate of the standard error, leading to confidence intervals that
are too narrow and p-values that are too small [18]. Another drawback is that it is difficult to verify that
these decisions were indeed based on the blinded data, rather than the unblinded dataset. As such, we
do not consider trials which use subjective decision rules as being fully pre-specified.

Finally, we note that in some instances adaptive analysis strategies can lead to biased estimates or
incorrect standard errors even when decision rules are fully deterministic; this typically occurs when the
decision rule is correlated with the size of the treatment effect or its standard error. Some examples of
this are available in the following references [18-20]. Therefore, caution should be applied when
considering adaptive strategies, even if deterministic decision rules are planned.

Example
We now illustrate our framework in an example. Consider the following analysis section from a trial
protocol for a continuous outcome measured at multiple follow-up time-points:

“Primary analyses will be undertaken on an intention-to-treat basis, including all participants as
randomised, regardless of treatment actually received. The [intervention group] will be compared with
the [control group] using a planned contrast of change from baseline to the week 12 endpoint ... using a
mixed-model repeated measures analysis. Stratification variables will be evaluated and retained in
analyses where they are measured as significant or quasi-significant. Transformation of [outcomes],
including categorisation, may be undertaken to meet distributional assumptions and accommodate outliers.”

Evaluating whether the analysis approach is fully pre-specified
This analysis approach meets our first two points; it was described in the trial protocol before recruitment began, and consists of a single overall analysis strategy.

For our third point, the analysis approach covers three analysis aspects (population, analysis model, covariates), however it does not specify how missing data will be handled. We can guess that patients with missing outcome data at certain follow-up time-points will be excluded from the analysis at those time-points, however this is not entirely clear.

For our fourth point, there is insufficient detail for a third party to independently replicate the analysis model; there are numerous ways to implement a mixed-model repeated measures analysis (for instance, different approaches to specifying random-effects, or different correlation structures to model the correlation between outcomes from the same patient), and it is not clear which approach the authors intend to use.

For our fifth point, the authors plan to use adaptive analysis strategies for two components; which covariates to include in the analysis, and whether to transform the outcome (and if so, which transformation to use). In both instances, there are no deterministic decision rules on how the final analysis approach should be decided (e.g. for covariates, there is no definition of what quasi-significant means), which would allow the analyst to subjectively choose the approach based on the final trial data.

Therefore, the specified analysis approach could allow the analyst to implement a number of different analysis strategies (relating to handling of missing data, the analysis model, covariates, and transformation of the outcome) and present the most favourable results. As such, this approach cannot be considered fully pre-specified.

**Modifying the analysis approach so it is fully pre-specified**

We can make this approach fully pre-specified by resolving the issues relating to points 3-5 above. First, we could explicitly state that patients with missing outcome data at certain follow-up time-points will be excluded from the analysis at these time-points. Second, we could provide additional information on how the analysis model will be implemented; for instance, we could specify a linear mixed-effects model with an unstructured correlation matrix for observations at different time-points, estimated using restricted maximum likelihood. We could supplement this description by including the planned statistical code to remove any ambiguity from our description (see below for example Stata code).

Finally, we need to resolve the issues around the adaptive analysis strategies related to the stratification variables and the transformation of the outcome. In this scenario, it is unlikely that the adaptive strategies are necessary, or even beneficial. All stratification variables should be included in the model regardless of statistical significance, as failure to do so can lead to incorrect confidence intervals and p-values [21, 22]. Furthermore, linear regression models are usually very robust to violations of distributional assumptions [23], and transformation can lead to issues of interpretability (in particular, categorisation could lead to a substantial reduction in power [24]). Therefore, the simplest way to resolve this issue is to remove the adaptive part, and use a strategy which includes all stratification variables in the model and does not consider transformations of the outcome. If the adaptive strategy was deemed necessary, then a deterministic decision rule would need to be specified, for example by
giving the exact p-value threshold for retaining stratification variables in the model (though we note this approach can be problematic even if fully pre-specified [18]).

Incorporating these changes, we could re-write the planned analysis strategy as follows:

*Primary analyses will be undertaken on an intention-to-treat basis, including all participants as randomised, regardless of treatment actually received. Participants with missing outcome data at certain time-points will be excluded from the analysis at these time-points. The [intervention group] will be compared with the [control group] using a planned contrast of change from baseline to the week 12 endpoint and will be fit using a linear mixed-model which includes outcomes at all time-points in the model. The model will use an unstructured correlation matrix for observations at different time points, and will be fit using restricted maximum likelihood. The model will include treatment group, the stratification variables, and the time point as fixed factors. This analysis will be implemented using the following Stata code:*

```
mixed outcome treat_group strat1 strat2 i.timepoint || patient_id:,
   res(unstructured, t(timepoint)) noconstant reml
```

*Where ‘outcome’ refers to the primary outcome, ‘treat_group’ to the treatment arm, ‘strat1’ and ‘strat2’ refer to the stratification variables, ‘patient_id’ is a unique ID for participant, and ‘timepoint’ refers to the follow-up time-point.*

We note that Stata automatically excludes time points with missing outcomes from the analysis, and so does not require additional code to perform this step. Further, we note that the above strategy is not necessarily the optimal statistical approach, but is used simply to illustrate how the original approach could be fully pre-specified.

**Discussion**

In clinical trials, it is important to assess whether investigators have pre-specified their statistical methods in advance, and whether they have followed what they said. Inadequate pre-specification or deviations from the pre-specified approach can allow investigators to perform multiple analyses and selectively report the most favourable. The Pre-SPEC framework provides guidance on how to ensure statistical methods are fully pre-specified to an extent that does not allow investigators subjective flexibility in which analyses to perform or report. This framework is consistent with the principles outlined in the SPIRIT and ICH-E9 guidelines; a comparison is provided in the supplementary material.

We do note that there are sometimes good reasons for investigators to change their statistical methods during the course of the trial, for instance because of an advance in statistical methodology or implementation of new methods in statistical software packages. Changes are acceptable, provided they are explained and justified [15]; however, a complete description of what was planned is necessary for readers to evaluate to what extent changes may have affected results, and whether the changes were justified.

It is sometimes argued that statistical methods, even for a trial’s primary outcome, can go in a stand-alone statistical analysis plan, rather than in the protocol. However, statistical analysis plans are
infrequently made publicly available and are often written after the trial has started. We therefore agree with the recommendations of the SPIRIT and ICH-E9 guidelines which state that the statistical methods for a trial’s primary outcome should be fully pre-specified in the trial protocol.

In conclusion, the Pre-SPEC framework can be used to ensure that statistical analyses are fully pre-specified. It is consistent with the principles outlined in SPIRIT and ICH-E9 and should increase statistical rigour and transparency in clinical trials.
Table 1: Common issues in pre-specifying statistical analysis approaches in clinical trial protocols

| Issue                                                                 | Problems associated with issue                                                                 | Aspect                                      | Estimated prevalence |
|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|---------------------------------------------|----------------------|
| Omitting an aspect of the analysis approach                          |Investigators could run multiple analyses, and selectively report the most favourable            |Analysis population:                        | 27-47%              |
|                                                                      |                                                                                                |Analysis model:                             | 11-20%              |
|                                                                      |                                                                                                |Covariates:                                 | 27%                 |
|                                                                      |                                                                                                |Missing data:                               | 66-77%              |
| Insufficient detail around an aspect of the analysis approach        |                                                                                                                                                        |Analysis population:                        | 64%                 |
|                                                                      |                                                                                                                                                        |Analysis model:                             | 42%                 |
|                                                                      |                                                                                                                                                        |Covariates:                                 | 23%                 |
|                                                                      |                                                                                                                                                        |Missing data:                               | 17%                 |
| Analysis approach allows some aspects of the final analysis to be subjectively chosen based on trial data |                                                                                                                                                        |Analysis model:                             | 19%                 |
|                                                                      |                                                                                                                                                        |Covariates:                                 | 8%                  |
| Multiple analysis approaches specified, without one being identified as the primary |Investigators could selectively report the most favourable result, or to elevate its importance compared to less favourable results. |Analysis population:                        | 11%                 |
|                                                                      |                                                                                                |Analysis model:                             | 11%                 |
|                                                                      |                                                                                                |Covariates:                                 | 9%                  |
|                                                                      |                                                                                                |Missing data:                               | 2%                  |

*a Based on references [5] and [2]

*b 15/99 protocols gave insufficient detail around how they planned to implement multiple imputation, 2/99 protocols but gave insufficient detail around their planned inverse probability weighting procedure

Box 1 – Framework for pre-specifying a statistical analysis strategy (Pre-SPEC)

| Description               | Description                                                                                                           |
|---------------------------|----------------------------------------------------------------------------------------------------------------------|
| Pre-specify before recruitment | Pre-specify the analysis strategy before recruitment to the trial begins.                                            |
| Single analysis strategy  | Specify a single primary analysis strategy.                                                                          |
| Plan all aspects          | All aspects of the planned analysis should be covered, including analysis population, statistical model, covariates, and handling of missing data. |
| Enough detail             | Provide sufficient detail to allow a third party to independently perform the analysis (ideally through statistical code). |
| Choices made deterministically | For adaptive analysis strategies which use the trial data to inform some aspect of the analysis, use deterministic decision-rules that prevent analysis choices being driven by results. |
References

1. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conference on Harmonisation E9 Expert Working Group. Statistics in medicine. 1999;18(15):1905-42.
2. Chan AW, Hrobjartsson A, Jorgensen KJ, Gotzsche PC, Altman DG. Discrepancies in sample size calculations and data analyses reported in randomised trials: comparison of publications with protocols. BMJ. 2008;337:a2299.
3. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Annals of internal medicine. 2013;158(3):200-7.
4. Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:e7586.
5. Greenberg L, Jairath V, Pearse R, Kahan BC. Pre-specification of statistical analysis approaches in published clinical trial protocols was inadequate. Journal of clinical epidemiology. 2018;101:53-60.
6. Abraha I, Cherubini A, Cozzolino F, De Florio R, Luchetta ML, Rimland JM, et al. Deviation from intention to treat analysis in randomised trials and treatment effect estimates: meta-epidemiological study. BMJ. 2015;350:h2445.
7. Dwan K, Altman DG, Clarke M, Gamble C, Higgins JP, Sterne JA, et al. Evidence for the selective reporting of analyses and discrepancies in clinical trials: a systematic review of cohort studies of clinical trials. PLoS medicine. 2014;11(6):e1001666.
8. Dworkin JD, McKeown A, Farrar JT, Gilron I, Hunsinger M, Kerns RD, et al. Deficiencies in reporting of statistical methodology in recent randomized trials of nonpharmacologic pain treatments: ACTTION systematic review. Journal of clinical epidemiology. 2016;72:56-65.
9. Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Dore C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. Jama J Am Med Assoc. 2017;318(23):2337-43.
10. Grant S, Booth M, Khodyakov D. Lack of pre-registered analysis plan allows unacceptable data mining for and selective reporting of consensus in Delphi studies. Journal of clinical epidemiology. 2018.
11. Nuesch E, Trelle S, Reichenbach S, Rutjes AW, Burgi E, Scherer M, et al. The effects of excluding patients from the analysis in randomised controlled trials: meta-epidemiological study. BMJ. 2009;339:b3244.
12. Page MJ, McKenzie JE, Forbes A. Many scenarios exist for selective inclusion and reporting of results in randomized trials and systematic reviews. Journal of clinical epidemiology. 2013;66(5):524-37.
13. Porta N, Bonet C, Cobo E. Discordance between reported intention-to-treat and per protocol analyses. Journal of clinical epidemiology. 2007;60(7):663-9.
14. Saquib N, Saquib J, Ioannidis JP. Practices and impact of primary outcome adjustment in randomized controlled trials: meta-epidemiologic study. BMJ. 2013;347:f4313.
15. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. PLoS medicine. 2010;7(3):e1000251.
16. Committee for Human Medicinal Products. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials, Step 2b.; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/08/WC500233916.pdf.
17. Morris TP, Kahan BC, White IR. Choosing sensitivity analyses for randomised trials: principles. BMC medical research methodology. 2014;14:11.
18. Raab GM, Day S, Sales J. How to select covariates to include in the analysis of a clinical trial. Controlled clinical trials. 2000;21(4):330-42.
19. Freeman PR. The performance of the two-stage analysis of two-treatment, two-period crossover trials. Statistics in medicine. 1989;8(12):1421-32.
20. Kahan BC. Bias in randomised factorial trials. Statistics in medicine. 2013;32(26):4540-9.
21. Kahan BC, Morris TP. Reporting and analysis of trials using stratified randomisation in leading medical journals: review and reanalysis. BMJ. 2012;345:e5840.
22. Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. Statistics in medicine. 2012;31(4):328-40.
23. Wang B, Ogburn EL, Rosenblum M. Analysis of covariance (ANCOVA) in randomized trials: More precision and valid confidence intervals, without model assumptions. Biometrics. 2019.
24. Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ. 2006;332(7549):1080.
| Pre-SPEC framework | SPIRIT                                                                 | ICH-E9                                                                 | Comment                                                                                                                                                                                                 |
|--------------------|-----------------------------------------------------------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pre-specify before recruitment to the trial begins | • “The planned methods of statistical analysis should be fully described in the protocol”<br>• “The protocol should indicate explicitly each intended analysis comparing study groups. An unambiguous, complete, and transparent description of statistical methods facilitates execution, replication, critical appraisal, and the ability to track any changes from the original pre-specified methods.” | • “For each clinical trial contributing to a marketing application, all important details of its design and conduct and the principal features of its proposed statistical analysis should be clearly specified in a protocol written before the trial begins.” (p5)<br>• “When designing a clinical trial the principal features of the eventual statistical analysis of the data should be described in the statistical section of the protocol. This section should include all the principal features of the proposed confirmatory analysis of the primary variable(s) and the way in which anticipated analysis problems will be handled.” P23-24 | Both SPIRIT and ICH-E9 state the planned statistical analysis approach should be pre-specified in the protocol. ICH-E9 explicitly states this should be done before the trial begins; SPIRIT does not state this explicitly, but it is implied given that the first version of the protocol must be completed before the trial begins. |
| Specify a single primary analysis strategy. | • “Results for the primary outcome can be substantially affected by the choice of analysis methods. When investigators apply more than one analysis strategy” | • “The primary analysis of the primary variable should be clearly distinguished from supporting analyses of the primary or secondary variables.” p28 | Both SPIRIT and ICH-E9 state explicitly that a single main analysis strategy should be identified. |
for a specified primary outcome, there is potential for inappropriate selective reporting of the most interesting result. The protocol should prespecify the main (“primary”) analysis of the primary outcome…”

- “When both unadjusted and adjusted analyses are intended, the main analysis should be identified (Item 20a).”

| Plan all aspects of the analysis (including analysis population, statistical model, covariates, and handling of missing data) | “The protocol should prespecify the main (“primary”) analysis of the primary outcome (Item 12), including the analysis methods to be used for statistical comparisons (Items 20a and 20b); precisely which trial participants will be included (Item 20c); and how missing data will be handled (Item 20c).”
- “It is important that trial investigators indicate in the protocol if there is an intention to perform or consider adjusted analyses, explicitly specifying any

| | “The set of subjects whose data are to be included in the main analyses should be defined in the statistical section of the protocol.” P24
- “The decision to transform key variables prior to analysis is best made during the design of the trial on the basis of similar data from earlier clinical trials. Transformations (e.g. square root, logarithm) should be specified in the protocol and a rationale provided, especially for the primary variable(s).” p27
- “The statistical section of the protocol should

SPIRIT explicitly states that the analysis population, analysis model, covariates, handling of missing data, and any other relevant aspects should be specified. ICH-E9 explicitly states that the analysis population, statistical model, covariates, and use of transformations for key variables should be specified.
variables for adjustment and how continuous variables will be handled.”

• “Protocols should explicitly describe which participants will be included in the main analyses (e.g., all randomised participants, regardless of protocol adherence) and define the study group in which they will be analysed (e.g., as randomised).”

• “The protocol should also state how missing data will be handled in the analysis and detail any planned methods to impute (estimate) missing outcome data, including which variables will be used in the imputation process (if applicable).”

• “Finally, different trial designs dictate the most appropriate analysis plan and any additional relevant information that should be included in the protocol. For example, cluster, factorial, crossover, and within-person randomised trials specify the hypotheses that are to be tested and/or the treatment effects which are to be estimated in order to satisfy the primary objectives of the trial. The statistical methods to be used to accomplish these tasks should be described for the primary (and preferably the secondary) variables, and the underlying statistical model should be made clear. Estimates of treatment effects should be accompanied by confidence intervals, whenever possible, and the way in which these will be calculated should be identified. A description should be given of any intentions to use baseline data to improve precision or to adjust estimates for potential baseline differences, for example by means of analysis of covariance.”

• “All effects to be fitted in the analysis (for example in analysis of variance models) should be fully specified... . The same considerations apply to the set of
| Requirement                                                                 | Description                                                                                                                                                                                                 |
|----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Require specified statistical considerations, such as how clustering will be handled in a cluster randomised trial. | Covariates fitted in an analysis of covariance. “p28

- “The primary variable(s) is often systematically related to other influences apart from treatment. For example, there may be relationships to covariates such as age and sex, or there may be differences between specific subgroups of subjects such as those treated at the different centres of a multicentre trial. In some instances an adjustment for the influence of covariates or for subgroup effects is an integral part of the planned analysis and hence should be set out in the protocol. Pre-trial deliberations should identify those covariates and factors expected to have an important influence on the primary variable(s), and should consider how to account for these in the analysis in order to improve precision and to compensate for any lack of balance between treatment groups.” P28

- “It is important that trial investigators indicate in the

- “The decision to transform key variables prior to analysis is best made

Both SPIRIT and ICH-E9 state that certain aspects of the analysis should be

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Enough detail should be provided so that a third
party could independently perform the analysis

protocol if there is an intention to perform or consider adjusted analyses, explicitly specifying any variables for adjustment and how continuous variables will be handled."

- “Protocols should explicitly describe which participants will be included in the main analyses (e.g., all randomised participants, regardless of protocol adherence) and define the study group in which they will be analysed (e.g., as randomised).”
- “The ambiguous use of labels such as “intention to treat” or “per protocol” should be avoided unless they are fully defined in the protocol. ... Other ambiguous labels such as “modified intention to treat” are also variably defined from one trial to another.”
- “The protocol should also state how missing data will be handled in the analysis and detail any planned during the design of the trial on the basis of similar data from earlier clinical trials. Transformations (e.g., square root, logarithm) should be specified in the protocol and a rationale provided, especially for the primary variable(s).”

p27

- “The statistical section of the protocol should specify the hypotheses that are to be tested and/or the treatment effects which are to be estimated in order to satisfy the primary objectives of the trial. The statistical methods to be used to accomplish these tasks should be described for the primary (and preferably the secondary) variables, and the underlying statistical model should be made clear. Estimates of treatment effects should be accompanied by confidence intervals, whenever possible, and the way in which these will be calculated should be identified. A description should be given of any intentions to use explicitly or fully described (e.g. analysis population, covariates, handling of missing data, etc).
| methods to impute missing outcome data, including which variables will be used in the imputation process (if applicable).” | baseline data to improve precision or to adjust estimates for potential baseline differences, for example by means of analysis of covariance.” P27 |
| • “All effects to be fitted in the analysis (for example in analysis of variance models) should be fully specified... . The same considerations apply to the set of covariates fitted in an analysis of covariance.” p28 |
| • “The primary variable(s) is often systematically related to other influences apart from treatment. For example, there may be relationships to covariates such as age and sex, or there may be differences between specific subgroups of subjects such as those treated at the different centres of a multicentre trial. In some instances an adjustment for the influence of covariates or for subgroup effects is an integral part of the planned analysis and hence should be set out in the protocol. Pre-trial deliberations should identify those covariates and factors expected to have an... |
| Adaptive analysis strategies should use deterministic decision rules | • “It is important that trial investigators indicate in the protocol if there is an intention to perform or consider adjusted analyses... It may not always be clear, in advance, which variables will be important for adjustment. In such situations, the objective criteria to be used to select variables should be prespecified.” | • “The particular statistical model chosen should reflect the current state of medical and statistical knowledge about the variables to be analysed as well as the statistical design of the trial. All effects to be fitted in the analysis (for example in analysis of variance models) should be fully specified, and the manner, if any, in which this set of effects might be modified in response to preliminary results should be explained.” p28 | SPIRIT advocates objective decision rules in a single specific instance (if covariates are to be chosen based on trial data). ICH-E9 states that the way the analysis might be modified in response to preliminary results should be specified. To the extent that adaptive analysis strategies are mentioned, both imply that pre-specified deterministic decision rules should be used. |