Author's response to reviews

Title: Three Steps to Writing Adaptive Study Protocols in The Early Phase Clinical Development of New Medicines

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Author's response to reviews: see over
Dear Dr Mangiameli,

I am pleased to resubmit the revised version of Manuscript ID 8129169471252146: “Three Steps to Writing Adaptive Study Protocols in The Early Phase Clinical Development of New Medicines” as a Correspondence article as recommended by the editor.

The comments of the reviewers were highly insightful and enabled us to improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers as well as your own comments.

**Reviewer: Weili He**

1. Reviewer’s Comment:

   This article attempts to define a universally acceptable terminology and describe a process of writing an adaptive study protocol for the early phase development of new medicines. However, it’s somewhat confusing to also mention in the abstract that “Adaptive study design avoids the delays associated with the creation and authorization of substantial protocol amendments.” Dragalin defined an adaptive trial (AD) as a multistage study design that uses accumulating data to decide how to modify aspects of the study without undermining the validity and integrity of the trial. The essential components of an AD trial include that changes are made by pre-specified algorithm(s) and not on an ad hoc basis and that adaptation is a design feature and not a remedy for poor planning. Therefore, adaptations made during the study should be pre-specified. Adaptations that were made during the study but were not pre-specified may lead to operational biases that should not be encouraged. Regardless of an adaptive design or regular study protocol, changes in study conducts outside of what a protocol described will result in protocol amendments.

   Authors’ response:

   We thank you for your considered comments on the definition of adaptive trials, the importance of potential adaptations being study design features and not ad-hoc
decisions or a remedy for poor planning. We full-heartedly agree with these statements and references, which we have also referred to in our manuscript [1].

Our paper describes protocol writing for early phase clinical trials. These trials are exploratory in nature and therefore typically hypothesis forming, not hypothesis testing. Statistical analysis of these exploratory trials is descriptive. Our paper does not aim to deal with statistical aspects of adaptive study design for confirmatory, hypothesis testing clinical trials.

The process we describe for study design/protocol writing aims to give an order to what happens anyhow during the course of early phase exploratory studies: evolving data requires frequent adaptations of study conduct which in turn often require protocol amendments (substantial or non-substantial). The more inflexible a protocol is written, the more substantial protocol amendments are required to deal with necessary changes, and the higher becomes the administrative regulatory burden. In our manuscript the term substantial protocol amendments has been used as defined in European legislation [5]. Substantial protocol amendments require Competent Authority (CA) and Research Ethics Committee (REC) approval whereas non-substantial amendments do not and can be implemented without delay.

To bring order to the necessary adaptation processes, to increase flexibility and to reduce administrative regulatory burden our manuscript proposes the following approach:

- To clearly specify in the protocol what adaptations can be made and the limits of each individual potential adaptation. We propose to do this in a systematic way and easy to review format as laid out in Table 1. The remit of adaptations is thereby categorised and clearly pre-defined. Adaptations outside the ones specified in Table 1 are not encouraged.
- Adaptations within the specifications given in Table 1 are non-substantial and in the UK do not require CA/REC review/approval. They can be documented in non-substantial protocol amendments or administrative protocol change documents, depending on sponsors’ policies. They are authorised by sponsor and investigator and can be implemented within hours, if necessary.
- Adaptations outside the specifications given in Table 1 are substantial and do require CA/REC review/approval. They must be documented in substantial protocol amendments. They must be authorised by the Competent Authority, Ethics Committee as well as sponsor and investigator. Time to implementation has been shown to take 5 weeks. Figure 1 provides a schematic of this process and the distinction between substantial and non-substantial protocol amendments.
- We have referenced a previous publication on the time savings of adaptive study design. [10].

Actions taken:

We have re-written the abstract to address your comment regards the confusing sentence. We have reviewed the entire manuscript in light of your comment and made relevant adjustments to make the point about pre-defined adaptations clearer,
to clearly distinguish between substantial and non-substantial amendments and to clarify the exploratory, hypothesis-forming nature of the studies described.

2. **Reviewer’s Comment:**

Although the EMA reflection paper on AD trials and FDA draft guidance on AD trials focused on confirmatory trials, the guiding principle on key factors an adaptive trial study protocol need to include should apply to early study AD study protocols as well. Specifically, details not just vague languages regarding the adaptation features, algorithms for adaptations, decision rules, and other related information should be pre-specified in the study protocol or the DMC charter. If that’s the case, there should not be a need to amend the protocols later on based on adaptations outside of the boundaries and control mechanisms.

**Authors’ response:**

We fully agree with your comment that all (1) adaptive features, algorithms for adaptations and their limits and (2) decision rules should be pre-specified in the study protocol (or a charter). The purpose of this manuscript is to provide templates for doing this within the study protocol and those templates are very specific:

- Table 1 requires exact description of every potential adaptation and every adaptation’s limit. As this is a template, it will need to be considered and adapted for each individual study when the protocol is written. To give an example:

**Template:**

<table>
<thead>
<tr>
<th>Adaptive Study Design Category</th>
<th>Adaptive Features</th>
<th>Boundaries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Dosing regimens may be determined or adapted in accordance with pharmacokinetic (PK), pharmacodynamic (PD), safety and tolerability data (as applicable) collected up to the decision making time-point. The term dosing regimen includes (1) the dose level administered, (2) the frequency of dosing and (3) the duration of dosing, i.e. the number of doses administered. Accordingly these can be adjusted individually or in combination.</td>
<td>1. Maximum starting dose</td>
<td></td>
</tr>
<tr>
<td>2. The number of dosing regimens investigated may be adjusted.</td>
<td>2. Maximum dose or exposure increment for each dose/exposure escalation step</td>
<td></td>
</tr>
<tr>
<td>3. Maximum (mean) exposure</td>
<td>3. Maximum (mean) exposure</td>
<td></td>
</tr>
<tr>
<td>5. Minimum/maximum treatment duration</td>
<td>5. Minimum/maximum treatment duration</td>
<td></td>
</tr>
<tr>
<td>6. Permissibility of dosing regimen adaptation within and/or between cohorts</td>
<td>6. Permissibility of dosing regimen adaptation within and/or between cohorts</td>
<td></td>
</tr>
<tr>
<td>7. Minimum/maximum number of dosing regimens to be investigated, safety and tolerability permitting</td>
<td>7. Minimum/maximum number of dosing regimens to be investigated, safety and tolerability permitting</td>
<td></td>
</tr>
<tr>
<td>8. Dose/exposure relationships</td>
<td>8. Dose/exposure relationships</td>
<td></td>
</tr>
</tbody>
</table>
Adaptive Study Design Category | Adaptive Features | Boundaries
---|---|---

between discrete parts of umbrella protocols (e.g. between SAD and MAD parts).

The following provides an example how this section of Table 1 will look for a real protocol:

1A Investigational Medicinal Product/Dose

<table>
<thead>
<tr>
<th>Adaptive Study Design Category</th>
<th>Adaptive Features</th>
<th>Boundaries</th>
</tr>
</thead>
</table>
| **Dosing regimen** | 1. Dosing regimens may be determined or adapted in accordance with pharmacokinetic (PK), pharmacodynamic (PD), safety and tolerability data (as applicable) collected up to the decision making time-point. The term dosing regimen includes (1) the dose level administered, (2) the frequency of dosing and (3) the duration of dosing, i.e. the number of doses administered. Accordingly these can be adjusted individually or in combination.  
2. The number of dosing regimens investigated may be adjusted. | 1. The starting dose for Part A of the study will not exceed 5 mg.  
2. The dose increments between the dose levels 1 to 2 in Part A will be no more than 5-fold.  
3. The dose increments between the dose levels 2 to 3 in Part A will be no more than 4-fold.  
4. The dose increments between the dose levels 3 to 4 and 4 to 5 in Part A will be no more than 3-fold.  
5. The first dose level in Part B will not exceed the doses previously explored in Part A with acceptable safety and tolerability, i.e. a dose level at which no study specific criteria stopping dose progression and/or escalation were met.  
6. The dose increments between the dose levels in Part B will be no more than 2-fold.  
7. The PK-derived exposure limit defined in section X of this protocol will not be exceeded.  
8. The maximum individual dose currently supported is 50 mg given every day. Dose escalation can proceed in accordance with the protocol defined dose escalation and toxicity rules up to this dose level. Individual Doses exceeding 50 mg given every day require MHRA approval of a substantial amendment presenting the necessary documentation supporting these dose levels. A protocol amendment will not be required as long as dose escalation |
As you can see there is no vagueness about the predefined adaptations whatsoever.

- Similarly the templates provided for decision rules (Figure 2, Toxicity Rules and Figure 3, Study Progression Rules) need to be populated with relevant study specific rules as outlined in the manuscript section “Step 3” under the heading “Three steps to writing an early phase adaptive protocol”. E.g.

Template:

**Study Progression Rules**

The elements of study progression rules which should be incorporated in an adaptive study protocol are:

(3) Minimum data reviewed at each decision making time-point

   (a) Nature of the data (PK, PD, safety and tolerability (reviewed in accordance with toxicity algorithm, see Figure 2)

   (b) Number of subjects

   (c) Post-dose review time period

“Real-life” example:

**Study Progression Rules**

(3) The minimum data reviewed at each decision making time-point will be

   (a) All PK, PD, safety and tolerability data (reviewed in accordance with toxicity algorithm, see Figure 2)

   (b) For a minimum of 6 subjects (i.e. 4 subjects on IMP)

   (c) For a minimum of 48 hours post last dose

With regards to toxicity rules, again the template is populated with the actual numbers of subjects who can experience defined grades of reversible or irreversible toxicities (in defined system organ classes) before any pre-defined actions need to be taken. These actual numbers will be different from compound to compound and from protocol to protocol.
With regards to protocol amendments, the implementation of adaptive features still needs to be documented so that “for every study participant there is a valid and reproducible study plan” as stated in our manuscript. This can be done by way of non-substantial amendment or administrative change to the protocol. The writing, submission and authorisation of substantial protocol amendments by the CA/REC is however avoided and this avoids the related study delays (please refer to our response to Comment 1).

Actions taken:

We have reviewed the entire manuscript in light of your comment and the amendments made in relation to your Comment 1 also serve to clarify issues relating to this Comment 2. We have been asked by the Editor to submit this as a correspondence article, i.e. to keep it as short as possible. Therefore there is currently no scope to include “real life” examples as the above ones, but we now refer to a recently accepted poster presentation which we have added to the references [2]. The study described in the poster presentation is an example for the practicability of the principles set out in this manuscript.

3. Reviewer’s Comment:

In summary, this reviewer is not certain whether the proposed protocol template languages for adaptive early trials will reduce the need for protocol amendments, if details, rather than vague languages, regarding specific adaptations in the study are not suggested to be included in the study protocol. In addition, languages such as these in Section on How to document adaptive changes to the protocol, “During the course of an adaptive study, decisions are made on study conduct and protocol leading to changes of the originally planned protocol. These changes need to be fully documented.” may add to the confusion.

Authors’ response:

The above sentences have been amended in the revised manuscript as follows:

“All changes to the protocol, resulting from the implementation of pre-defined adaptive features, need to be fully documented.”

We hope that our responses to your previous comments have addressed your concerns relating to the specificity of pre-defined protocol adaptations and to documentation, i.e. substantial protocol amendments versus non-substantial amendments/administrative protocol change documents.

Reviewer: Frank Bretz

1. Reviewer’s Comment:

The manuscript is of potential interest, but there are concerns. The manuscript would benefit if a concrete case studies would be incorporated to illustrate the concepts.
The authors state that they will include "examples from projects we have authorised and performed in the UK" (p. 2), but I could not locate those examples. Otherwise this manuscript remains fairly vague.

1. **Authors’ response:**

Thank you very much for your comment with which we completely agree. It is similar in nature to comments made by Weili He and we would like to refer you to our above responses.

Table 1 summarises template “examples” of all types of adaptions we have used in “projects authorised and performed in the UK”. We have chosen this approach, so that users can consider and choose from this wide range and adapt Table 1 (and the decision rules) to their specific compound and study protocol. We have shown in our above responses how this looks in a real protocol.

We do have good case studies which we could refer to in the manuscript, however as stated above, we are currently restricted in the word count due to the manuscript classification. We have however amended the manuscript and now refer to a recently accepted poster presentation [2] providing an example of a relevant study (see above) and further publications are in preparation.

2. **Reviewer’s Comment:**

On p. 7 the authors state that "the data is usually reviewed in a blinded fashion". What do you mean by this? Are you really suggesting that in a SAD study dose escalation decisions (mostly based on safety data to determine the maximum tolerable dose) do not make use of the information on which treatment the patient was randomized to (placebo or drug, in most cases)? This would be opposite to standard practices. Please clarify.

**Authors’ response:**

Thank you for your comment which we believe may refer to standard practices for late phase confirmatory trials, during with an independent data safety monitoring committee reviews un-blinded data. The investigator(s) and sponsor remain blinded to avoid bias.

The standard practice for early phase exploratory trials however is that the data is reviewed blinded by a safety review committee consisting of Principal Investigator and Sponsor’s representatives. The purpose of these review meetings is strictly focussed to make dose escalation decisions in line with the pre-defined protocol decision rules. The determination of the maximum tolerated dose is in our experience extremely rarely an aim of these studies.

The review is conducted at pre-specified decision making time-points. The data reviewed at these time points is also pre-defined in the protocol and so are the decision makers and the documentation required (please see above responses). Therefore the review process itself requires CA/REC approval.
It is usually safety data - that can be linked to individual volunteers - and blinded PK and PD data that is reviewed. Blinded PK/PD data can be compared to what was anticipated from pre-clinical and earlier clinical data and modelled for upcoming dosing regimens. PK/PD data is coded and cannot be linked to individual volunteers. This is to avoid un-blinding and biasing investigator and sponsor who are also the decision makers for these early exploratory studies.

Un-blinding for the type of studies referred to in our manuscript occurs after database lock when the entire study has been completed and the database is final. This is to ensure that all data queries are resolved and a blind review of the data is conducted in an unbiased fashion before the database is locked. The only incidence when un-blinding during such a study may occur is a medical emergency or medically important event which would normally constitute a SUSAR and put the study on hold (in accordance with the pre-defined study toxicity rules and clinical trials regulation).

3. Reviewer’s Comment:

I have the impression that this manuscript uses the term “adaptive design” not in the sense of, for example, the FDA (2010) guidance document. Please clarify whether you are indeed referring to adaptations incorporated via protocol amendments. As mentioned above, standard practice makes use of un-blinded data and revisions not previously planned and made or proposed after an un-blinded interim analysis raise major concerns about study integrity.

Authors’ response:

The term “adaptive design” is used in accordance with FDA (2010) Guidance for industry: adaptive design clinical trials for drugs and biologics. As it is stated in chapter III, paragraph A of the FDA guidance, all modifications suggested in this paper refer to prospectively planned aspects of the study, pre-specified in the protocol. For further detail we refer to the above responses. Data review and decision making is also pre-defined and performed in a blinded fashion as outlined above.

With regards to your point on protocol amendments, adaptations to study design and conduct need to be documented, whether the protocol is adaptive or not. As elaborated above, all adaptations to non-adaptive protocols meeting the regulatory definition of a substantial protocol amendment need to be made and authorised as such. Amendments to adaptive protocols can be documented and implemented without delay as non-substantial protocol amendments or administrative protocol change documents, as long as they are within the pre-defined adaptive scope of the protocol. Substantial protocol amendments are only required if the adaptations are outside the pre-defined protocol specifications.

4. Reviewer’s Comment:

On p. 5 you state “in an early phase protocol it is advantageous to make a wide range of possible adaptations available” and further on p. 11 “there is no further interaction with the CA/REC so long as the study proceeds within the protocol’s
adaptive specifications”. Thus, my understanding is then that in future I will design my protocols as general as possible (i.e. with all sorts of adaptations I can think of) and since then I don’t expect any major changes to the protocol I can proceed with my study without further interactions. Is this your suggestion? I would have great difficulties with this proposal.

Authors’ response:

We appreciate your comment and have revised the context of the above quoted statement to read:

“The categories and nature of adaptive changes that may potentially be required due to evolving data are largely predictable. Therefore, in an early phase protocol it is advantageous to make a full range of these potential adaptations available of which all necessary ones can be implemented without delay.”

Whilst it is correct that in the UK there is “there is no further interaction with the CA/REC so long as the study proceeds within the protocol’s adaptive specifications”, this is not due to the fact that the protocols are written as general as possible. On the contrary, these protocols are only approved by the CA/REC because every potential adaptation is pre-defined in the protocol with its limits and there are clear rules in place to control the study. As stated in the manuscript: “Regulatory acceptability of an adaptive trial depends on the setting of safe boundaries rather than the permutations and details of potential adaptations to the study conduct.”

The authors have regulatory and clinical pharmacology backgrounds. The manuscript is based on real experience authorising and performing studies in the UK. On this basis we believe that the approach described in our manuscript is logical and sound from a regulatory and scientific perspective.

Authors’ summary in response reviewers’ comments:

This manuscript is aimed to introduce a very simple, three step process of condensing all necessary text relating to early phase adaptive protocol design into one table (Table 1) and two flow-charts (Figures 2 and 3), rather than having this text scattered across study protocols in an unsystematic fashion which is otherwise often the case.

The second aim is to provide template text for potential adaptive features, their limits and study control mechanisms, which can be adapted by template users to their specific study. A wide range of pre-defined adaptive protocol features reduces the need to write substantial protocol amendments and the significant regulatory burden related to their review and approval. In the authors’ experience gathered since 2006, these aims have been achieved by using the approach described in our manuscript.

We believe that “real life” examples on how the templates can be adapted and case studies would make this manuscript very much longer and not necessarily clearer. We have added a reference to a contemporaneous publication and plan the publication of several studies which have been conducted successfully using the process described in this paper.
We very much appreciate the reviewers’ valuable comments which have helped us to revise the manuscript. The comments also indicate that a lively discussion may follow publication of this manuscript which may well stimulate further development of the use of adaptive design in a wider early phase research community.

We feel that the manuscript can make a significant contribution to the study design and writing of early phase exploratory study protocols. We strongly believe that it will be of interest to researchers and sponsors as this approach ultimate supports a more efficient early development of new medicines. We hope that the revisions in the manuscript will be sufficient to make our manuscript suitable for publishing in The BMC Medical Research Methodology.

Yours sincerely,
Dr Ulrike Lorch MD FRCA FFPM