Adaptive Early Phase Clinical Trials in the UK

Jorg Taubel
Bonn, October 30th, 2014
1. Adaptive Study Design

One or more decision points are built into the trial design; The subsequent conduct following that decision point depends on the data observed to that point ...

‘without undermining the validity and integrity of the trial’

‘Changes are made “by design”, and not on an ad-hoc basis; therefore, adaptation is a design feature aimed to enhance the trial, not a remedy for inadequate planning.’

Benefits

Continuous learning and early decision making
Adjusting the study design taking into account data as it emerges

Research is directed towards

*Meaningful assessments*

*Collection of relevant data*

Research is

*Safe*

*Ethical*

*Cost effective*
2. Umbrella (Fusion/Combined) Protocol

A number of conventional studies contained in one single study protocol:

- Single Ascending Dose
- Multiple Ascending Dose
- Food Effect
- Age/Gender comparisons
- Intensive cardiac safety assessments
- Ethnic comparisons
- Drug Drug Interactions
- Proof of Concept
- Patient populations
Time saved

• Is greatest when *combining* Adaptive Designs with Umbrella Studies
Example: Phase 1/2 study design and progression plan

Part 1
SAD in HNV

Part 2
MAD in HNV

Part 3
MD in XXX Patients

POC – in patients

XXX Patients

2015

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Finally, you are reminded that a favourable opinion from the Ethics Committee is also required before this trial can proceed; changes made as part of your amended request may need to be notified to the Ethics Committee.

Yours sincerely,

Clinical Trials Unit
MHRA

For information only:
The sponsor is commended for their approach in the protocol to the risks in the study and approach to the adaptive design, in particular Table 1. This significantly aided review of the application and such an approach would be encouraged in future clinical trial applications.

Authorisation of your clinical trial is subject to the following condition(s):

- Any change to the latest period of the drug substance will require the prior submission and approval of a substantial amendment.
- Any extension to the shelf life of the drug product will require the prior submission and approval of a substantial amendment.

If these conditions are met, the trial is authorised and you do not need to respond to this letter. If your trial does not meet these conditions, your trial does not have authorisation and therefore you can not proceed with the trial. You must inform the MHRA immediately if the trial does not meet the above conditions. All changes to the terms and conditions of this trial must be made as a request for a substantial amendment to this clinical trial authorisation.

The authorisation is effective from the date of this letter although your trial may be suspended or terminated at any time by the Licensing Authority in accordance with regulation 31. You must notify the Licensing Authority within 90 days of the trial ending.
Adaptive Early Phase Studies

Q: What gets approved?
A: The worst case!
   – Same as any SAD study lowest vs. MTD
Risk Assessments & Safety

Toxicity Rules

Adaptive Boundaries

Continuous Assessment

Study Progression Rules

Avoidance of unnecessary exposure

Collection of necessary data only

Flexibility to change if safety requires
What’s the trick?

How can we write an adaptive study protocol that is sufficiently detailed, clear, systematic whilst allowing for flexibility and evolution?

How can the layout facilitate ethical and regulatory review?
Simplicity
Clinical Study Protocol
Clinical Study Protocol

A set of rules and decision trees rather than detail:

<table>
<thead>
<tr>
<th>Adaptive Features</th>
<th>(Safety) Boundaries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1  2

3

Study Progression Rules

Toxicity Rules

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Three steps to writing adaptive study protocols in the early phase clinical development of new medicines

Ulrike Lorch1*, Martin O’Kane2 and Jorg Taubel1

Abstract
This article attempts to define terminology and to describe a process for writing adaptive, early phase study protocols which are transparent, self-intuitive and uniform. It provides a step by step guide, giving templates from projects which received regulatory authorisation and were successfully performed in the UK. During adaptive studies evolving data is used to modify the trial design and conduct within the protocol-defined remit. Adaptations within that remit are documented using non-substantial protocol amendments which do not require regulatory or ethical review. This concept is efficient in gathering relevant data in exploratory early phase studies, ethical and time- and cost-effective.

Keywords: Adaptive study design, Adaptive protocol, Protocol writing, Early phase clinical research
## Adaptive Features and their Boundaries

<table>
<thead>
<tr>
<th>Protocol Area</th>
<th>Adaptive features</th>
<th>(Safety) Boundaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigational Medicinal Product (IMP) / Dose</td>
<td>Dosing regimens&lt;br&gt;IMP formulation/mode of administration</td>
<td>Starting dose&lt;br&gt;Maximum exposure&lt;br&gt;Maximum dose/exposure increments&lt;br&gt;Maximum treatment frequency/duration</td>
</tr>
<tr>
<td>Timing / Scheduling</td>
<td>Overlap&lt;br&gt;Sentinel/Sub-groups</td>
<td>Minimum data requirements for progression&lt;br&gt;Reference to study specific toxicity rules</td>
</tr>
<tr>
<td>Study Participants</td>
<td>Sample size (cohort size, No. of cohorts)&lt;br&gt;Selection criteria</td>
<td>Minimum/maximum size and No. of cohorts&lt;br&gt;Nature, direction and extent of adaptability of selection criteria</td>
</tr>
<tr>
<td>Assessments</td>
<td>Safety, PK, PD, exploratory samples and assessments can be adjusted in nature, timing and extent</td>
<td>Minimum data requirements for progression&lt;br&gt;Maximum extent</td>
</tr>
<tr>
<td>Methods/Analysis</td>
<td>Methods and or analysis may be optional</td>
<td>Nature, timing, extent and purpose of adaptability&lt;br&gt;Minimum data requirements for progression</td>
</tr>
</tbody>
</table>
Controls: Toxicity Rules

Grade 1
- Expected*
  - Reversible‡
  - Frequency†
- Unexpected*
  - Not reversible‡
  - Frequency†

Grade 2
- Non-serious
  - Expected*
    - Reversible‡
    - Frequency†
  - Unexpected*
    - Not reversible‡
    - Frequency†
- Non-serious
  - Expected*
    - Reversible‡
    - Frequency†
  - Unexpected*
    - Not reversible‡
    - Frequency†

Grade 3
- Unexpected*
  - Reversible‡
  - Frequency†
  - Not reversible‡
  - Frequency†
- Non-serious
  - Unexpected*
    - Reversible‡
    - Frequency†
    - Not reversible‡
    - Frequency†

Grade 4-5
- Serious
  - Study suspended

Study Progression
- Continue

Either one or a combination of the following:
1. Continue
2. Explore dosing regimen further
3. Suspend further escalation/exploration
4. Explore lower exposure dosing regimen

*As defined in the study protocol
‡Within pre-determined observation period
†Per system Organ Class

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Definition/description of toxicity

- CTCAE
- Sentiment vs. medical assessment criteria

1. The most extensive catalogue of AE available (based on MedDRA)
2. Not in any way exclusive to cancer trials
3. Providing a consistent numerical system to assess AE severity
4. Allows the use of “template” toxicity criteria
   (NB: protocol needs to include wording that this has been checked and confirmed.)

Common Terminology Criteria for Adverse Events (CTCAE)
Version 4.0
Published: May 28, 2009 (v4.03: June 14, 2010)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

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Safety Review Committee

- Membership
- Authority
- Frequency
- Reviews typically performed on blinded data incl. PK/PD
- Minimal data requirements

Inclusion of wording in the protocol to set out the principles/processes
The detailed content of these elements depend on the study design, the IMP PK/PD profile and its anticipated risks and are described in the study protocol.
Controls: Study Progression Rules

- Single Dose 1: Minimum PK/PD, Minimum Safety
- Single Dose 2: Minimum PK/PD, Minimum Safety
- Single Dose 3: Minimum PK/PD, Minimum Safety
- Single Dose 4: Minimum PK/PD, Minimum Safety
- Multiple Dose 1: Minimum PK/PD, Minimum Safety
- Patient Dose 1: Minimum PK/PD, Minimum Safety
- Ethnic Comparison Dose 1: Minimum PK/PD, Minimum Safety
- Food Effect Dose
- Drug-Drug Interaction

= Exposure/Dose escalation
= Progression to another study part
Study progression: Practical Aspects

• Decision makers
• Site infrastructure
  – Training & Delegation
  – CMC
  – eCRF
• Protocols
• Informed Consent
Q: How do we deal with adaptive changes? Do they need to be disseminated to REC/MHRA?

Q: In case of a combined protocol (i.e. the umbrella protocol), do we have to submit the results from the individual parts of the study before we are allowed to move forward to the next part?

Q: Do we need any authorizations before proceeding?

A: No, unless the criteria for a substantial amendment are met.

*Medicines and Healthcare products Regulatory Agency (MHRA) / National Research Ethics Service (NRES), UK

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Informed Consent

- Divide Informed Consent for ‘umbrella’ studies into relevant distinct parts/forms
- Give headlines of what may change and the boundaries
- Avoid description of technical or scheduling details
- Describe maximum potential risks and inconveniences
Before May 2005:
Clinical Trials in healthy volunteers were not regulated by UK law (Medicines Act 1968)

Local Ethics Committees would provide the only form of legitimation reviewing the science, ethics and non-clinical data to support human (trial) use.

2005 onwards:
Regulatory approval is required (The Medicines for Human Use (Clinical Trials) Regulations 2004 transposing Directive 2001/20/EC1 into UK law.) as well as a favourable opinion from a Research Ethics Committee.
Regulators

Science
Toxicology
CMC

Ethics
All Matters relating to consent
“Although RECs must be assured about the planned ethical conduct and anticipated risks and benefits of any proposed research, they are not responsible for enforcement if the research turns out to be unsafe or is not carried out as agreed. This responsibility rests with the relevant regulators or comparable bodies, as well as with the researchers’ employer and sponsor and with the care organisations where the research takes place.[...].”

“A REC need not reconsider the quality of the science, as this is the responsibility of the sponsor and will have been subject to review by one or more experts in the field (known as ‘peer review’). The REC will be satisfied with credible assurances that the research has an identified sponsor and that it takes account of appropriate scientific peer review.”

“A REC can expect to rely on established mechanisms for ensuring the proper conduct of the research at individual sites.”

“Where others have a regulatory responsibility, a REC can expect to rely on them to fulfil it. If the law gives another body duties that are normally responsibilities of a REC according to this document, RECs do not duplicate them. For example, the Medicines and Healthcare products Regulatory Agency has the primary legal responsibility for considering the safety of the research it regulates.”

experience
For us ...

... it works!
It was not born over night ...

- We started with a few adaptive features at first
- Most studies use few out of a “menu” of features listed in a protocol
- We began to structure the various features into a template process
- We engaged with other stakeholders
Published Experience

Eur J Clin Pharmacol
DOI 10.1007/s00228-011-1176-3

CLINICAL TRIAL

The practical application of adaptive study design in early phase clinical trials: a retrospective analysis of time savings

U. Lorch · K. Berelowitz · C. Ozen · A. Naseem · E. Akuffo · J. Taubel

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Abstract

Background The interest in adaptive study design is evident from the growing amount of clinical research employing this model in the mid to later stages of medicines development. Little has been published on the

Introduction

The aim of using adaptive study design in early phase clinical trials is to develop new medicines in a safe, efficient and cost effective manner, progressing rapidly from first
29 Adaptive Studies in five Years

Over time, we got better doing it!

Lorch et al.
The practical application of adaptive study design in early phase clinical trials: a retrospective analysis of time savings.
Example: Phase 1/2 study design and progression plan

Part 1
SAD in HNV

Part 2
MAD in HNV

Part 3
MD in XXX Patients

Adaptive Protocol Features

Adaptive Timing Features

SAD#1
SAD#2
SAD#3
SAD#6-JPN
SAD#4
SAD#7-JPN
SAD#5
SAD#8-JPN

MAD #1
MAD #2
MAD #3
MAD #4

POC – in patients

XXX Patients

Feb Mar Apr May Jun Jul Aug Sep 2015

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HOW ADAPTIVE STUDY DESIGN CAN ENRICH AN EARLY PHASE MULTIPLE ASCENDING DOSE STUDY

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Introduction

The use of adaptive designs in clinical research is attractive due to its flexibility, efficiency and economy. Adaptive designs are valuable during the early phases of drug development as they help optimize the selection of relevant data towards Proof of Concept, whilst maintaining patient centricity and minimizing trial time and cost of development (1). Recently we have published an article with a step by step guide on how to set adaptive protocols in the early phases development of new medicines (2).

To illustrate the benefits of this concept, we present results from a randomized, double-blind, placebo-controlled, multiple ascending dose study to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of **Sulfuramide** in healthy male subjects following daily dosing for 7 days. **Sulfuramide** is a chemically stable, synthetic sulfonamide, structurally resembling in Levofloxacin (Levaquin) which is being developed as a potential treatment to prevent the progression of early stage juvenile rheumatoid arthritis.

The adaptive design allowed us to immediately react to emerging PK and tolerability data and to adjust the study design and conduct within a very short timeframe. As all changes were within the adaptive design scope, we were able to make changes to dosing regimens and assessments and we introduced a new approach to dealing with the need for Regulatory or Ethics Committee submissions.

Aim

The aim of this double-blind, placebo-controlled, single ascending dose study was to determine the maximum tolerated dose (MTD) and to assess the safety, tolerability and PK of multiple doses of **Sulfuramide** over 7 days.

Methods

Study Design

Eighteen (18) subjects (17 male: 1 female) entered the study. All subjects completed the study and were included in the safety and PK analyses. All cohorts in volunteers received dosing for 7 days. Cohorts 1 and 2 received 500 mg **Sulfuramide** once daily. Cohorts 3 and 4 received 300 mg twice daily.

For Cohorts 2 and 3 the protocol was amended to increase the dose to 750 mg daily. On Days 6 and 7 of Cohort 4, standardized meals were served at the following times: breakfast (approximately 90 minutes prior to dosing in the fast state or approximately 1 hour post-dose in the fast state), lunch (approximately 4 hours post-dose) and dinner (approximately 7 hours post-dose) and dinner (approximately 13 hours post-dose and approximately 11 hours post-dose, respectively).

Pharmacokinetic Sampling

Sampling was adjusted for Cohorts 2 and 3, adding a second PK sampling day to assess the effects of food and adjusting sampling time points on all blindly PK sampling days 1, 4 and 7.

Statistical Analysis

The results of patient factors (age, weight, height, gender) were analyzed by descriptive statistics. PK data was limit for each subject along with univariate statistical including arithmetic and geometric means, standard deviation (SD), minima, maximum and medians, and area under the curve (AUC), PK data was fitted by univariate statistics including arithmetic and geometric means, SD, minimum, maximum, medians and CV.

Results

Following a single ascending dose study, the main objectives of the study were to determine a therapeutic, well tolerated multiple dosing regimen of **Sulfuramide**. A daily dose of 400 mg was expected to be the therapeutic dose and well tolerated within the exposure limits set out by the FDA and EMA regulatory agencies.

The PK profile in treated condition, summarized the profile of the SAD study (Figure 3A). However, in Cohort 1, the expected C\textsubscript{max} was exceeded the expected limit of 135 ng/ml. Therefore, on day 1, we found that C\textsubscript{max} was reached at around 5 hours post-dose, with no PK samples had been scheduled for Cohort 1. As a result, the actual C\textsubscript{max} exceeded that required by regulatory guidelines. This was accompanied by pharmacological adverse events (Figure 3B) which led to a lower C\textsubscript{max} and to improve tolerability, food was introduced before dosing in Cohort 2 and 3. At 500 mg per day with food (Cohort 2) C\textsubscript{max} still exceeded the maximum limit. Therefore in Cohort 3 the dose was split into 2 500 mg, with food. C\textsubscript{max} was delayed around 2 hours, 200 mg per day **Sulfuramide** in fed condition (Cohort 5) produced a C\textsubscript{max} between 81.62 ng/ml at 12.21 40 ng/ml, C\textsubscript{max} stayed below 100 ng/ml, to 300 ng/ml. This is considered a therapeutic and within limits exposure.

Discussion

The practical application of relevant adaptive features led to the determination of a suitable dosing regimen with good tolerability for **Sulfuramide** sulfonamide plasma concentrations. As all adjustments were within the adaptive scope of the protocol, no regulatory or Ethics Committee submissions were required and the study could proceed with minimal and fixed scope of studies which led to increased efficiency of drug development.

References


Acknowledgements & conflicts of Interest

The authors are employees of Richmond Pharmacology Limited (RPL). RPL received funding from Sorgent to conduct the study. There are no conflicts of interest to declare.

Example 2

A complete Phase I development in one protocol:

- SAD
- MAD
- Food
- Elderly postmenopausal women
- Ethnic bridging*

*The slide presented during the meeting stated “DDI” which was a typing error. My apologies.
Example 3

Terminating futile efforts early (new mode of action)

– CNS side effects caused various amendments, including substantial amendments
– The AEs were subsequently established as “class effects”
– The project was terminated as soon as practicable in the shortest period of time at a very low cost
Conclusions + Points for Discussion

• Adaptive features enhance the scientific value of trials; they optimally use a fixed budget
• Umbrella protocols allow time savings mostly by overlapping conventional trials; they must be adaptive in order to achieve this
• Protocols must be very clearly structured
• Sponsor and the clinical site must have experience gained over time (starting with less complex protocols at first)
"If we knew what it was we were doing, it would not be called research, would it?"

- Albert Einstein