A spoonful of data helps the medicine go down: Purposeful collection of clean and reproducible trial data

Webinar
Oct 20\textsuperscript{th}, 2022
Program

**Introduction:** Speaking a common language

**Part I: Early planning and communication**
- Fictitious case presentation
- Panel discussion: planning
- Panel discussion: communication

**Part II: Essential data and documentation in clinical trials**
- What is essential data
- Theoretical examples
- Panel discussion: essential data/documentation
Speaking a common language

The Tower of Babel by Pieter Bruegel the Elder (1563)
## Types of trials

<table>
<thead>
<tr>
<th>Trial type</th>
<th>Sponsor</th>
<th>Funding</th>
<th>Intended use</th>
<th>Industry role</th>
<th>Filing intent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic trial</td>
<td>* Non industry</td>
<td>* Publication clinical practice guidance</td>
<td>None</td>
<td><strong>X</strong></td>
<td></td>
</tr>
<tr>
<td>Investigator-Initiated trial</td>
<td>* Mixed</td>
<td>* Publication clinical practice guidance</td>
<td>Drug provisioning</td>
<td><strong>X</strong></td>
<td>* exceptions exist</td>
</tr>
<tr>
<td>Academic-Industry Collaborative trial</td>
<td>* Industry</td>
<td>Licensing</td>
<td>Full funding Drug provisioning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Industry Trial</td>
<td>* Industry</td>
<td>Licensing</td>
<td>Full responsibility Ownership of the trial</td>
<td></td>
<td><strong>✓</strong></td>
</tr>
</tbody>
</table>
Complexity of trial development

- **Designing the trial**
  - Investigational Plan: Defining the
    - Patient population
    - Objectives
    - Endpoints
    - Statistical methodology and analysis plan
  - Protocol and trial document development
    - Patient-facing documents
    - Defining
      - Essential documents
      - Essential data
      - Inspection readiness
  - Funding
    - Investigator Brochure
- **Developing the trial**
  - Database development
    - Ethics and regulatory approvals
  - Protocol and trial documents approval
    - Including DSMB/IRB charters
    - Evaluate companion diagnostic/Investigational Device Exemption
- **Trial conduct**
  - Site set up
  - Recruitment
  - Data collection
  - Study monitoring
  - Pharmacovigilance
  - Data management
  - Interim data analyses
  - On-going oversight of trial progress
  - Drug supply
    - +/- distribution
  - Evaluate need for protocol amendments
- **End of study**
  - Data analyses
  - End of Study Report
  - Study Publications
  - Study closure and archiving
  - Data-sharing including:
    - Essential data
    - IPD
    - Inspection readiness
  - Data and document review
- **Filing for MA/drug approval**
  - Preparation of Clinical Study Report
  - Compilation of application submission package
  - Determine effectiveness and safety; Benefit: Risk assessment
  - Inspections and audits
On risk, quality and safety in clinical trials

“Risk, quality and safety” can have different meaning for partners involved in trial development.

- The risk of patients harm vs the risk of incomplete data vs commercial risks to an asset
- data can be of high quality by:
  - being correct
  - being completely traceable
- safety of a subject in a trial vs safety in trial procedures
EMA and FDA guidelines

Risk based strategies in trial development?

Guidelines on how to run trial more efficiently and effectively, striving towards trials that result in the minimum but complete data packages to answer the trial question while ensuring subject safety and GCP compliance.
Case study 1: Early planning

GRU gene mutations in 25% of adult miniosarcoma cases

Both *Nefario pharmaceuticals* and *Perfect pharmaceuticals* have developed a GRU inhibitor
How to find out if your GRU inhibitor for miniosarcoma is relevant in other tumor entities? In paediatrics?

- Literature
- Animal data
- Toxicity data

- Early collaboration, possibly with an academic partner?
Case study 1: Early planning

GRU gene mutations in 25% of miniosarcoma (adult) cases and it is the oncogenic driver in 78% of all minioblastoma (paediatric)

Both Nefario pharmaceuticals and Perfect pharmaceuticals have developed a GRU inhibitor

What’s next?
Quiz 1: When is the latest you must plan your pediatric studies?
Legislation requiring paediatric investigations

Pre clinical

Phase I

Phase II

Phase III

Pediatric study plan

Modifications/amendments

PREA required studies

End of adult phase II

Agreed iPSP

Approval

Submission and review

Post marketing

Adult PK available

Compliance on PIP studies

Marketing authorisations

Agreed Paediatric Investigational Plan

Modifications as needed

HTA approval
Treatment of minioblastoma

• Nefario pharmaceuticals
• Grunitinib
• Fully focused on the mionosarcoma target
• Assumes target is irrelevant for paediatric cancer

• Perfect pharmaceuticals
• Drunitinib
• Focused on miniosarcoma, but explored and identified minioblastoma in the pre-clinical phase
Engagement of stakeholders

• Fully focused on the miniosarcoma target

• Engaged community of miniosarcoma experts + patient advocates

• Engaged community of miniosarcoma experts + patient advocates

• Engaged paediatric experts through international trial consortia of minioblastoma while preparing adult phase I
Quiz 2: When to engage regulators?
Panel composition

**Academia**

Pam Kearns (University of Birmingham)

Beth Fox (St. Jude Children’s Research Hospital)

**Industry**

Elly Barry (Former Pfizer, now Day One)

**Patient advocates**

Donna Ludwinski (Solving Kids Cancer)

**Regulators**

Martha Donoghue (FDA)

Dominik Karres (EMA)

Kim Pietsch (EMA)
While running the adult phase I/II

- Regulators refuse waiver/deferral
- Scrambles to identify potential other uses for Grunitinib

- Adult trial with age inclusivity, recruits a 14 year old with miniosarcoma
- Paediatric phase I in minioblastoma in preparation with academic partner
Quiz 3: What communication style in between partners in trial development would be most productive?
Closed vs open communication

• Writes own paediatric trial protocol to evaluate safety (copy of adult program)

• Initiated discussion with regulators together with academic experts

• Full disclosure on paediatric requirements with all partners
Treatment of minioblastoma

- Paediatric phase I/II trials has shown safety
- One patient with minioblastoma with unknown mutations status for GRU included -> no signal
- Paediatric development stopped
- Limited safety data available at completion of adult trial (14 year old miniosarcoma)
- Academic partner runs phase I/II trial in GRU mutated minioblastoma; 45% of patients respond
- Strong signal of activity in paediatric indication
Recommendation

Communication should be:

• continuous and transparent
• Inclusive (regulators, academic experts, patient advocates)
• Remain considerate of commitments (e.g. PIP contents)
Panel composition

**Academia**
- Pam Kearns (University of Birmingham)
- Beth Fox (St. Jude Children’s Research Hospital)

**Patient advocates**
- Donna Ludwinski (Solving Kids Cancer)

**Regulators**
- Martha Donoghue (FDA)
- Dominik Karres (EMA)
- Kim Pietsch (EMA)

**Industry**
- Elly Barry (Former Pfizer, now Day One)
Essential data/essential documentation

Essential documents and data individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements and allow for a risk/benefit assessment.
How to identify data/documentation essential in a clinical trial?

Is there a list?
• Yes
  • International Committee on Harmonization Guidance for Industry: E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)

Does just checking the list make you “fit for filing”? 
• No
  • If it is not in the list, but necessary for the evaluation, it is essential: the rationale is of importance and can be discussed
  • How documents are managed is also an important consideration
We compiled a list of:

- Essential documents: with a rationale why (not) to collect them in your trial
- Essential CRF data elements: with considerations on when and how to collect them

www.accelerate-platform.org/education
What makes data essential in a trial?

• Consider a phase I/II trial of Drunitinib for minioblastoma

  • Given that children will be treated only as a “last resort”, when curative treatment options have been exhausted
  • Given that Drunitinib causes minimal prolongation of cardial QT interval in sensitive patients...
Quiz 4: What level of medication use do we need to collect?
Concomitant medication in a phase I dose finding study

- Probability fatal arritmia due to long QT
  - Unlikely
- Potential impact:
  - Huge on safety of subjects

- No compromise here: full details on current medication use?
Quiz 5: What level of previous medical history reporting is appropriate?
Panel composition

**Academia**
- Pam Kearns (University of Birmingham)
- Beth Fox (St. Jude Children’s Research Hospital)

**Patient advocates**
- Donna Ludwinski (Solving Kids Cancer)

**Industry**
- Elly Barry (Former Pfizer, now Day One)

**Regulators**
- Martha Donoghue (FDA)
- Dominik Karres (EMA)
- Kim Pietsch (EMA)
Previous history in a phase I dose finding study

• Heavily pre treated patient population
  • Highly complex data, exact previous history details probably obscure
• Is this helping ensure subject safety
  • Or is a good evaluation of organ toxicity at screening a better strategy?

• Pragmatic strategy is collection is permissable?
What makes data essential in a trial?

- Consider a phase II trial of the standard chemo backbone + Drunitinib for minioblastoma
  - Chemo backbone is well established and in use for over 20 years
  - Phase I/II monotherapy data on Drunitinib is available
Quiz 6: What level of adverse event reporting is required?
Panel composition

**Academia**
- Pam Kearns (University of Birmingham)
- Beth Fox (St. Jude Children’s Research Hospital)

**Patient advocates**
- Donna Ludwinski (Solving Kids Cancer)

**Regulators**
- Martha Donoghue (FDA)
- Dominik Karres (EMA)
- Kim Pietsch (EMA)

**Industry**
- Elly Barry (Former Pfizer, now Day One)
Thank you!

NEXT: With great trial needs comes great responsibilities: Delivering high quality data and successfully file an application

10 Nov
6-7:30pm CEST - 12-13:30pm EST