Master Protocols in Neonatal Infections:
Pharmacokinetic, Safety and Outcome Assessment

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Declaration of interests

• My employers have received funds for clinical studies from: Roche, Chiesi, Johnson & Johnson, Pfizer, EC FP7, NIHR, BLISS, MRC, AMR

• My employers receive funds for consultancy from Chiesi, BMS, Novartis, Shire, Janssen, Grunenthal

• Chair, European Network for Paediatric Research at the European Medicines Agency

• Co-Director, International Neonatal Consortium

• Coordinator, European Paediatric Clinical Trials Research Infrastructure
Topics

State of the art

• Systematic reviews of extant protocols

Components of a master protocol

Design of a master protocol
State of the art

Harmonisation in study design and outcomes in paediatric antibiotic clinical trials: a systematic review

Laura Folgori, Julia Bielicki, Beatriz Ruiz, Mark A Turner, John S Bradley, Daniel K Benjamin Jr, Theoklis E Zaoutis, Irja Lutsar, Carlo Giaquinto, Paolo Rossi, Mike Sharland

Components of a master protocol

Need alignment of:

Inclusion criteria
• EMA consensus statement etc.

Target groups
• Empiric / Confirmed / Rescue

Outcomes

Methodology
• Clinical / Microbiology / PK
Target groups

- Population
- Empiric
- Confirmed
- Rescue

Culture positive
Percentage of culture proven LOS in different countries

- EE
- GR
- IT
- TR
- SP
- LI

Culture proven
Clinical+other
# Target groups

<table>
<thead>
<tr>
<th>Target</th>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empiric</td>
<td>Complete</td>
<td>Post-randomisation imbalance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss of numbers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bacteria not known</td>
</tr>
<tr>
<td>Confirmed</td>
<td>Bacteria known (if culture positive)</td>
<td>Previous treatment may affect efficacy and safety</td>
</tr>
<tr>
<td></td>
<td>Enriched for infection</td>
<td>signals</td>
</tr>
<tr>
<td>Rescue</td>
<td>Bacteria known (if culture positive)</td>
<td>Previous treatment may affect efficacy and safety</td>
</tr>
<tr>
<td></td>
<td>Enriched for resistant bacteria</td>
<td>signals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical variation in timing</td>
</tr>
</tbody>
</table>
# Target groups

<table>
<thead>
<tr>
<th></th>
<th>Preterm</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- NEC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Meningitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- VAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- BPD</td>
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</tr>
</tbody>
</table>
Issues

Marked variation between settings in:

• Microbiology

• Standard of care

• Thresholds for moving between confirmed and rescue
  
  – Protocol deviations
Goals of a master protocol

Develop PK models

Percentage Attainment of a PK/PD target

Assess Efficacy

  • Clinical
  • Microbiological

Assess Safety

  • Descriptive
  • Causal
PK and PD data

Sample collection (generally acceptable)

Storage and transfer

Assays

TDM

Analysis

Warehousing

Covariates
Plasma concentration of meropenem by country
Safety data

Background events

• Prematurity

• Term conditions

Drug specific

• Predictable

• Unpredictable

Infection specific
Safety data

Background events

• Prematurity
• Term conditions

Drug specific

• Predictable
• Unpredictable

Infection specific

Definitions

Severity

Causality
Efficacy Outcomes

Components

• Alive or dead
• Resolution of clinical features
• Resolution of microbiological features
• No change in therapy
• No new microbiological concerns
Choice of outcomes

Issues include

- Feasibility
- Timing in the study
- Influence of co-medication (e.g. medicines with some G+ and G- activity)
- Utility
- Balance between pre and post approval
Difficulties with Efficacy as the primary outcome

Ascertainment

Culture negative cases

Other treatments

• especially before randomisation

Confirmed cases are not common

Specific resistant bacteria are rare
Master protocol designs: 1

<table>
<thead>
<tr>
<th>Design</th>
<th>Approach</th>
<th>Output</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each centre evaluates one antibiotic that is compatible with local needs</td>
<td>Each antibiotic is studied in several centres and in one or more target groups</td>
<td>Population PK model that incorporates covariates from multiple centres and target groups</td>
<td>Could be combined with PD targets</td>
</tr>
<tr>
<td>sites selected for the antibiotics they <strong>currently</strong> use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All antibiotics are studied consistently</td>
<td>Efficacy data also available</td>
<td>Safety surveillance could include all babies in the centre (with consent)</td>
</tr>
</tbody>
</table>
# Master protocol designs: 2

<table>
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<th>Output</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Each centre compares more than one antibiotic  
  • Sites selected according to the antibiotics they are **prepared to use** | Randomised for a single target group  
  • one of empiric, confirmed or rescue  
  • Could vary between centres according to preferences | Comparative data  
  • For target attainment  
  • For efficacy | Could be a comparison to standard of care  
  • which may differ  
 Could be a comparison between two agents |
| | Need to ensure adequate numbers of comparators | | Safety surveillance could include all babies in the centre (with consent) |
Key assumptions

Data can be pooled across sites

• PK warehouse

• Stratification by
  – Site
  – GA band
  – Target group

Common comparator

• May be difficult

• “Network analysis”
Conclusions

Master protocols can be developed

• PK data can be pooled

• Safety issues are generic to neonates

• Outcomes may be problematic

• Comparisons may be problematic

Please work with Europe and other jurisdictions