Design of Controlled Clinical Trials

by

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Sample Size

- The probability of erroneously claiming difference between groups (Type I errors or significance level). {wanted as small as possible}

- The probability of detecting a real difference between groups. (Detection level or 1 Type II error). {wanted as large as possible}

- Clinical relevant difference. How large should a difference be in order to be of clinical interest?

- Optimalisation of study design.

- Degree of heterogeneity in the study population.

- Observation methodology.
Designs of CCT’s

BETWEEN PATIENT DESIGNS
- Parallel group design
- Stratified design
- Factorial designs

WITHIN PATIENT DESIGNS
- Latin Square design
- Semi cross-over design
- Greaco Latin square design
- Multi-cross-over design
Between patient designs

- **Advantage**
  - Accepted by the authorities all over the world
  - Will always give information

- **Disadvantage**
  - Need a lot of patients
  - Might result in two or more groups which is not initially comparable
  - Predefined and standardized interventions and investigations
Cross-over design

The patients are equally allocated to one of two treatment sequences (A-B) or (B-A).

1. Registration period
2. Registration period

“Wash-out”
Greaco Latin Square Design

A-B-C
B-C-A
C-A-B

A-B-C  A-C-B
B-C-A  C-B-A
C-A-B  B-A-C
Multi cross over design

Diagram: 1. period 2. period 3. period 4. period 5. period 6. period
Combined MCO and Parallel group design
Within Patient Design

- **Advantage**
  - Reduces the needed number of patients
  - Able to discover small differences between interventions

- **Disadvantage**
  - The patient needs to be in the same condition at the start of every period
  - The number of patients in each group has to be absolutely the same.
  - The duration of the study might be too long
  - A wash-out period between each intervention sequence is needed
  - Predefined and standardized interventions and investigations
Designs of CCT’s

Adaptive designs
- Play-the-Winner design (PTW)
- Modified Play-the Winner design (MPTW)
- Randomized Play-the-Winner design (RPTW)
- Weighted Play-the-Winner design (WPTW)

Sequential designs
- Triangular finite and infinite
- Trapezium finite and infinite

Response surface designs
- Binomial plain design
- Iteration design (within patients)
- Pathway design (between patients)
Play-the winner Design

PAT 1  PAT 2  PAT 3  PAT 1  PAT 2  PAT 1  PAT 2

CHANGE OF TREATMENT

○: treatment A  ○: treatment B

○: success  ■: failure
Expression of the results from PTW

O. Reiersen et al.

Survival function $S(t)$

- Enoxaparin
- Dextran 70

Number of patients
Adaptive Design

**Advantage**
- To be performed during the daily routine.
- A controlling design, recording what happens in a real situation.
- The obtained study population will be close to the reference population.
- It is a family of design between Epidemiology and CCT.

**Disadvantage**
- Needs a large sample size.
- Not commonly accepted as a randomised controlled design.
Triangular finite Sequential Design
Example of sequential design
Sequential Designs

### Advantage
- Reduces the needed number of patients
- Discover during the trial if something unexpected or a dangerous situation occurs
- Stops the trial when the aim can be answered
- Can be combined with all kind of designs

### Disadvantage
- Have to be statistically monitored during the study
- Need special data software
- Need more than a basic knowledge of statistics
Response surface design

- **Advantage**
  - Can be used together with different other designs
  - Increase the information by a given number of laboratory animals
  - Reduce the number of laboratory animals without loss of information
  - The intervention is not prefixed but dependent on the results obtained at the last investigation
  - Makes the time for interventions and investigation stochastic
Selection of doses

Proportion

0,5

Dose level

0 1 2 3 4 5
Selection of doses

![Graph showing dose levels against proportion]

Dose level vs. Proportion

- Dose levels: 0, 0.5, 1, 2, 3, 4, 5
- Proportion: 0, 0.5, 1
Response surface design

- Aim: Dose finding studies
  - and Controlled clinical studies

- Background situation
  - With some prior knowledge
  - Without or limited knowledge
Response surface design with iteration

- In order to get similar power to that obtained by 16 animals in this design, 198 animals have to be included in a traditional design.
A general four level Response
Surface Pathway Design

Level 1
- m (400)
- m-m/2 (200)

Level 2
- m+m/2 (600)
- m-m/2 (200)

Level 3
- m+m/2+ m/4 (700)
- m-m/2+ m/4 (500)
- m-m/2-m/4 (300)

Level 4
- m+m/2+ m/4+ m/8 (750)
- m+m/2+ m/4-m/8 (650)
- m+m/2-m/4+ m/8 (550)
- m+m/2-m/4-m/8 (450)
- m-m/2+ m/4+ m/8 (350)
- m-m/2+ m/4-m/8 (250)
- m-m/2-m/4+ m/8 (150)
- m-m/2-m/4-m/8 (50)
The response Pathway of Yessotoxin expressed with dose levels and proportion of dead mice
The proportion of dead mice with 95% confidence intervals at different dose levels in the two comparative designs.

<table>
<thead>
<tr>
<th>Dose level (µg/kg.bw.)</th>
<th>Response surface design</th>
<th>Evenly distributed dose levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proportion of dead mice</td>
<td>Proportion of dead mice</td>
</tr>
<tr>
<td>700</td>
<td></td>
<td>100,0 (66,4 – 100,0)</td>
</tr>
<tr>
<td>600</td>
<td>77,8 (40,0 – 97,2)</td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>55,6 (21,2 – 86,3 )</td>
<td>55,6 (18,0 – 94,7 )</td>
</tr>
<tr>
<td>450</td>
<td>44,4 (13,7 – 78,8)</td>
<td></td>
</tr>
<tr>
<td>400</td>
<td>33,3 (7,5 – 70,1)</td>
<td></td>
</tr>
<tr>
<td>300</td>
<td></td>
<td>0,0 (0,0 – 33,6)</td>
</tr>
<tr>
<td>100</td>
<td></td>
<td>0,0 (0,0 – 33,6)</td>
</tr>
</tbody>
</table>
The response Pathway of DTX-2 with semi optimal (red) and optimal (blue) design expressed with doses and proportion of dead mice

<table>
<thead>
<tr>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
<th>Level 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 (4/5)(3/3)</td>
<td>600</td>
<td>650</td>
<td>675</td>
</tr>
<tr>
<td>500 (4/5)(3/3)</td>
<td>600</td>
<td>650</td>
<td>625</td>
</tr>
<tr>
<td>500 (4/5)(3/3)</td>
<td>600</td>
<td>650</td>
<td>575</td>
</tr>
<tr>
<td>500 (4/5)(3/3)</td>
<td>600</td>
<td>650</td>
<td>525</td>
</tr>
<tr>
<td>500 (4/5)(3/3)</td>
<td>600</td>
<td>650</td>
<td>475</td>
</tr>
<tr>
<td>500 (4/5)(3/3)</td>
<td>600</td>
<td>650</td>
<td>425</td>
</tr>
<tr>
<td>400 (4/7)(3/5)</td>
<td>550</td>
<td>575</td>
<td>375</td>
</tr>
<tr>
<td>400 (4/7)(3/5)</td>
<td>550</td>
<td>575</td>
<td>325 (1/9)(3/9)</td>
</tr>
<tr>
<td>400 (4/7)(3/5)</td>
<td>550</td>
<td>575</td>
<td>325 (1/9)(3/9)</td>
</tr>
<tr>
<td>400 (4/7)(3/5)</td>
<td>550</td>
<td>575</td>
<td>325 (1/9)(3/9)</td>
</tr>
<tr>
<td>400 (4/7)(3/5)</td>
<td>550</td>
<td>575</td>
<td>325 (1/9)(3/9)</td>
</tr>
</tbody>
</table>
The proportion of dead mice with 95% confidence intervals at different dose levels in the semi optimal and the optimal response surface pathway designs.

<table>
<thead>
<tr>
<th>Dose level (µg/kg.bw)</th>
<th>Semi optimal design</th>
<th>Optimal design</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proportion of dead mice</td>
<td>Proportion of dead mice</td>
</tr>
<tr>
<td>500</td>
<td>80,0 (28,4 – 99,5)</td>
<td>100,0 (29,2 – 100,0)</td>
</tr>
<tr>
<td>400</td>
<td>57,1 (18,4 – 90,1)</td>
<td>60,0 (14,7 – 94,7)</td>
</tr>
<tr>
<td>350</td>
<td>85,7 (42,1 – 99,6)</td>
<td>57,1 (18,4 – 90,1)</td>
</tr>
<tr>
<td>325</td>
<td>11,1 (0,3 – 48,3)</td>
<td>33,3 (7,5 – 70,1)</td>
</tr>
</tbody>
</table>
The five level response surface Pathway of DTX-2 with optimal design expressed with doses and proportion of dead mice
## Comparison of results

<table>
<thead>
<tr>
<th>Design</th>
<th>Dosed levels used (µg/kg bw)</th>
<th>Number of dead mice</th>
<th>Number of mice used</th>
<th>Estimation of LD$_{50}$ (µg/kg bw) with 95% confidence intervals in brackets</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSP$_A$-design</td>
<td>500</td>
<td>4</td>
<td>5</td>
<td>366 (316 – 424)</td>
</tr>
<tr>
<td>(Semi optimal)</td>
<td>400</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>350</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>325</td>
<td>1</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>RSP$_B$-design</td>
<td>500</td>
<td>3</td>
<td>3</td>
<td>355 (301 – 419)</td>
</tr>
<tr>
<td>(Optimal)</td>
<td>400</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>350</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>325</td>
<td>3</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Level 5</td>
<td>338</td>
<td>5</td>
<td>11</td>
<td>353 (310 – 402)</td>
</tr>
</tbody>
</table>

Comparison of results
Basic change in dose levels

Level 1
- m (400)
- m-m/2 (200)

Level 2
- m+m/2 (600)
- m-m/2 (200)

Level 3
- m+m/2+m/4 (700)
- m-m/2+m/4 (500)

Level 4
- m+m/2+m/4+m/8 (750)
- m+m/2+m/4+m/8 (550)
- m-m/2+m/4+m/8 (450)
- m-m/2+m/4+m/8 (350)
- m-m/2+m/4+m/8 (250)
- m-m/2+m/4+m/8 (150)
- m-m/2+m/4+m/8 (50)
From Fixed to Stochastic observation time or dose levels

<table>
<thead>
<tr>
<th>Number of dead mice</th>
<th>Level 2 ((m_2))</th>
<th>Level 3 ((m_3))</th>
<th>Level 4 ((m_4))</th>
<th>Level 5 ((m_5))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>(m_{1+} m_{1}/k)</td>
<td>(m_{2+} m_{1}/k^2)</td>
<td>(m_{3+} m_{1}/k^3)</td>
<td>(m_{4+} m_{1}/k^4)</td>
</tr>
<tr>
<td>1</td>
<td>(m_{1+} m_{1}/k^2)</td>
<td>(m_{2+} m_{1}/k^3)</td>
<td>(m_{3+} m_{1}/k^4)</td>
<td>(m_{4+} m_{1}/k^5)</td>
</tr>
<tr>
<td>2</td>
<td>(m_{1+} m_{1}/k^2)</td>
<td>(m_{2+} m_{1}/k^4)</td>
<td>(m_{3+} m_{1}/k^5)</td>
<td>(m_{4+} m_{1}/k^6)</td>
</tr>
<tr>
<td>3</td>
<td>(m_{1+} m_{1}/k)</td>
<td>(m_{2+} m_{1}/k^4)</td>
<td>(m_{3+} m_{1}/k^6)</td>
<td>(m_{4+} m_{1}/k^7)</td>
</tr>
<tr>
<td>4</td>
<td>(m_{2+} m_{1}/k^3)</td>
<td>(m_{3+} m_{1}/k^6)</td>
<td>(m_{4+} m_{1}/k^8)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(m_{2+} m_{1}/k^2)</td>
<td>(m_{3+} m_{1}/k^5)</td>
<td>(m_{4+} m_{1}/k^8)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(m_{3+} m_{1}/k^4)</td>
<td>(m_{4+} m_{1}/k^7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>(m_{3+} m_{1}/k^3)</td>
<td>(m_{4+} m_{1}/k^6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>(m_{4+} m_{1}/k^5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>(m_{4+} m_{1}/k^4)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
RSP design with stochastic interventions

Level 1

Level 2

Level 3

Level 4

400 (1/3)

600

500 (3/5)

525

475(4/7)

469(4/9)

300

200

500

550

525

525

500

488

482

463

450

400

450

425
Comparison of fixed and stochastic dose steps

<table>
<thead>
<tr>
<th>Design</th>
<th>Dosed levels used (µg/kg bw)</th>
<th>Number of dead mice</th>
<th>Number of mice used</th>
<th>Estimation of LD$_{50}$ (µg/kg bw) with 95% confidence intervals in brackets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four level RSP-design using a minimum number of mice and pre-fixed doses</td>
<td>400</td>
<td>1</td>
<td>3</td>
<td>446 (345 – 577)</td>
</tr>
<tr>
<td></td>
<td>450</td>
<td>5</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>600</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Four level RSP-design using a minimum number of mice and result-related doses</td>
<td>400</td>
<td>1</td>
<td>3</td>
<td>468 (389 – 563)</td>
</tr>
<tr>
<td></td>
<td>469</td>
<td>4</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>475</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

The use of Response Surface Pathway design in CCT and Laboratory Animal Research will:

1. Increase the information from a given number of animals
2. Reduce the number of animals without loss of information to 1/3
3. In order to optimize the design, the number of animals has to be reduced to a minimum at the first design level