Monitoring of Patient Recruitment in Surgical Trials

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Background

Facts:

114 trials, 1994-2002

• Only 31 % of RCT reach final recruitment goal

• Start to recruitment was delayed in 41 %

• Early recruitment problems in 63 %

McDonald AM et al: What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies
Consequences of poor recruitment

• Loss of time
• Underpowered trials - no significance
• Ethical question
• Increased costs

Recruitment:
Levels of influence

Did the study recruit well?

If study is recruiting, did the center recruit well?

If center is participating, did doctor recruit well?

If the patient is asked, did he/she consent?
Recruitment in surgical trials
Levels of influence

Patient: Less influence compared to drug trials. Important: patient informed consent.

Surgeon: Surgical skill and experience are essential. Convictions may have large influence. Training issue.

Center: Different surgical (house) standards may interfere with trial procedures. Education and training.

Study: Trial must address an important question for surgical practice.
SDGC: What we do

- Development and Design of RCT
- Management and Analysis of RCT
- Safety Management
- Registration and Publication of Clinical Trials
- Monitoring/Auditing
- Fund Raising
- Education

Recruited patients in SDGC trials 2003 - 2010
Balance of activities*

• 12 multicenter RCT
  Finished (3), FU (3), Recruiting (4), Starting 2011 (2)
  Funding: public (8) / industry (4, partial)

• 20 Systematic Reviews
  Finished (13), Ongoing (7). Funding: public (4), industry (1)

• > 2500 randomized patients in 130 hospitals

• 7 clinical investigator courses with >150 participants

• ca. 50 peer reviewed publications

* since 2004
German Surgical Network

CHIR-Net: 8 regional centers

Projected vs. real time

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Milestones</td>
<td>Quarter</td>
</tr>
<tr>
<td>First patient in</td>
<td>April</td>
</tr>
<tr>
<td>Last patient in</td>
<td>I</td>
</tr>
<tr>
<td>Patient follow-up</td>
<td>II</td>
</tr>
<tr>
<td>Data base closure</td>
<td>II</td>
</tr>
<tr>
<td>Data analysis</td>
<td>III</td>
</tr>
<tr>
<td>Biostatistical report</td>
<td>IV</td>
</tr>
<tr>
<td>Publication</td>
<td>IV</td>
</tr>
</tbody>
</table>

1 year behind schedule
Commitment of centers

ChroPac trial

<table>
<thead>
<tr>
<th>Center</th>
<th>Initiation</th>
<th>Months active</th>
<th>Expected* (patients/year)</th>
<th>Actual recruitment</th>
<th>Rate / year (%) actual/expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.10.09</td>
<td>13</td>
<td>30</td>
<td>6</td>
<td>18 %</td>
</tr>
<tr>
<td>2</td>
<td>08.10.09</td>
<td>13</td>
<td>15</td>
<td>9</td>
<td>55 %</td>
</tr>
<tr>
<td>3</td>
<td>19.05.09</td>
<td>18</td>
<td>60</td>
<td>35</td>
<td>39 %</td>
</tr>
<tr>
<td>4</td>
<td>16.11.09</td>
<td>12</td>
<td>8</td>
<td>5</td>
<td>63 %</td>
</tr>
<tr>
<td>5</td>
<td>22.09.10</td>
<td>2</td>
<td>15</td>
<td>1</td>
<td>40 %</td>
</tr>
<tr>
<td>6</td>
<td>18.03.10</td>
<td>8</td>
<td>10</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>7</td>
<td>01.09.09</td>
<td>14</td>
<td>5</td>
<td>3</td>
<td>51 %</td>
</tr>
<tr>
<td>8</td>
<td>18.11.09</td>
<td>12</td>
<td>10</td>
<td>5</td>
<td>50 %</td>
</tr>
<tr>
<td>9</td>
<td>14.01.10</td>
<td>10</td>
<td>5</td>
<td>6</td>
<td>144 %</td>
</tr>
<tr>
<td>10</td>
<td>02.11.09</td>
<td>12</td>
<td>3</td>
<td>2</td>
<td>67 %</td>
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<tr>
<td>Total</td>
<td></td>
<td></td>
<td>161</td>
<td>72</td>
<td>45 %</td>
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</table>

*recruitment was initially planned on 2 patients per week, actual rate in Nov 2010 was 1 patient per week.
Measures taken to improve recruitment

Standard

• Trial registration: ISRCTN38973832
• Newsletters
• Logo: ChroPac
• Publication of trial protocol: Trials 2010, 11:47
• Website http://www.chropac-trial.eu/
Measures taken to improve recruitment

Physicians
- Letter to 346 medical practitioners
- Letter to alumni

Medical conventions
- 5 / 2010 DGCH presentation at SDGC
- 9 / 2010 DGAV oral presentation
- 10 / 2010 Poster Mittelrhein. Chirurgen
- 11 / 2010 Additional Investigator Meeting
Measures taken to improve recruitment

Patients

- Arbeitskreis Pankreatektomierte

Lay persons

- Newspaper articles:
  - RNZ (Rhein-Neckar Zeitung)
  - Mannheimer Morgen
Measures taken to improve recruitment

Eligibility criteria

Specification of inclusion criterion communicated in Newsletter 3 and by monitors

(Amendment is necessary, if eligibility criteria are changed.)
Measures taken to improve recruitment

New participating centers

• Proposal: 11 centers
• 1 center called off participation
• 4 new centers in 1st round
• 5 further centers in 2nd round
• 15 centers have randomized patients to date
Difficult to get started

ChroPac: From initiation to first patient screened

Status: 10.05.2011

Time
Results: improved recruitment

<table>
<thead>
<tr>
<th>Time (in quarters)</th>
<th>Number of centers initiated</th>
<th>Number of centers recruiting</th>
<th>Number of patients recruited</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009 / II</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2009 / III</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>2009 / IV</td>
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<td>3</td>
<td>13</td>
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<tr>
<td>2010 / I</td>
<td>11</td>
<td>7</td>
<td>16</td>
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<td>8</td>
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<td>2010 / III</td>
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<td>9</td>
<td>13</td>
</tr>
<tr>
<td>2010 / IV</td>
<td>14</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>2011 / I</td>
<td>17</td>
<td>15</td>
<td>27</td>
</tr>
</tbody>
</table>

- Planned recruitment: 2 patients per week.
- Actual rate 11/2010: 1 patient per week.
- 1st quarter 2011: 2 patients per week.
Recruitment potential

HASTA trial: Patients screened – randomized

Have all potential patients been identified?
Screened?
Can the randomization rate be improved?

Trials 2011, 12:34
doi:10.1186/1745-6215-12-34
Good start and then …

TOPAR-pilot trial: Planned vs. real course

What happened here?

Market access of new drug (Cinacalcet) reduced number patients undergoing surgical treatment.

Recruitment time was prolonged from 18 to 43 months.

Trials 2007, 8:22
TOPAR-pilot: Actions taken

• Newsletters
• Contact participating centers
• Contact endocrine surgeons at annual meeting
• Send out material and invitations
• Investigator‘s meeting with interested centers
• 1 center closed
• 1 new center initiated
Improving recruitment

CLIVIT trial: Planned vs. real course

Measures taken:  
- 8 new centers initiated  
- 1 center closed  
- Widening of inclusion criteria  
  (amendment to trial protocol)

Trials 2006, 7:27  
doi:10.1186/1745-6215-7-27
Recruitment Planned Centers

First patient in: 05MAR04  last patient in: 29JUL08

Nr of center

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Date randomization

01/01/04 01/01/05 01/01/06 01/01/07 01/01/08 01/01/09

amount of patients

0 50 100 150 200 250 300 350 400 450 500 550

1 year

4 ½ years of recruitment instead of 3 years
Recruitment ahead of schedule

DISPACT trial: planned vs. real course

Clin Trials 2008 5: 534
DOI: 10.1177/1740774508096140

Results: Diener, MK et al
Lancet 2011;377:1514-22
Obstacles: Interim analysis

- Recruitment was stopped for adaptive interim analysis.
- Advance was lost and not regained.
- 4 centers did never restart recruitment.
- 2 new centers were activated.
- Timelines were met nonetheless.
Ready, ... go

PROUD trial: from initiation to first patient randomized

Status: 10.05.2011
SDGC experience: Prerequisites

- Clinically relevant trial question
- Optimal time point
- Simple trial design
- Professional trial management
- Portfolio of compensatory measures
Recruitment: success factors*

• Important research question
• Timeliness
• High research standard:
  - patients’ needs
  - potential to change clinical work
• Leadership of the PI
• Excellent communication skills
• Strong and efficient coordinating team

* MK Campbell, C Snowdon, D Francis, D Elbourne, AM McDonald, R Knight, V Entwistle, J Garcia, I Roberts, A Grant: Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study Health Technology Assessment 2007; Vol. 11: No. 48
Final conclusion

- Monitor recruitment closely
- Give feedback to centers regularly
- Analyze deviations from recruitment goals
- Identify principal cause(s)
- Have courage to adopt unpleasant measures
- Do not lose time to react

Stay active
Thank you

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