Osteosarcoma treatment in Europe and elsewhere is far from being centralized:
Lessons from EURAMOS-1 (NCT00134030)

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Klinikum Stuttgart - Olgahospital¹ and University Hospital Muenster², Germany; MRC Clinical Trials Unit³ & UCL Hospitals NHS Trust⁶, London, UK; Stanford University Medical Center, USA⁴; Norwegian Radium Hospital, Oslo, Norway⁵; IWK Health Centre, Dalhousie University, Halifax, Canada⁷

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EURAMOS Recruitment as of March 31, 2011

2,169 patients from 328 institutions in 17 countries*

Cumulative registrations overall

COG | 1,108 | 51.08
COSS | 506  | 23.33
EOI  | 439  | 20.24
SSG  | 116  | 5.35
Total | 2,169 | 100.00

Thanks to EURAMOS-CDC, MRC London

*USA incl. Puerto Rico. 4 COG centers in 3 other countries
EURAMOS target population 606.57 million
ca. 8.7% of world population

[Bar chart showing population distribution across countries]
Do countries achieve similar population-adjusted recruitment rates?
Recruitment / Country / Million population

EURAMOS mean 3.58

USA  |  GER  |  UK  |  CDN  |  AUS  |  NL  |  BE  |  CZ  |  HUN  |  SE  |  A  |  CH  |  DK  |  FIN  |  NOR  |  NZL  |  IRE
--- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | ---
3.09 | 5.11 | 4.88 | 2.26 | 1.19 | 5.9 | 4.62 | 0.88 | 2.37 | 3.07 | 4.7 | 4.81 | 8.1 | 3.17 | 0.99
Years recruiting

0 1 2 3 4 5 6
DE SE NO CH UK NL BE USA AUS CDN DK H NZL FI N A I RE CZ
Recruitment / Country / Million population per year with trial open

EURAMOS mean 0.60/year
DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 4 April 2001

on the approximation of the laws, regulations and administrative provisions of the Member States
relating to the implementation of good clinical practice in the conduct of clinical trials on
medicinal products for human use
Trial Approval

• National Competent Authorities
• Ethics Committees

• Regional Competent Authorities
• Science Funders
• Insurance Companies
• Learned Societies
• Drug evaluation bodies
• ............................................
• ............................................
Documentation to be held by investigator / institution for clinical trials

Detailed guidance for the principles of GCP in the conduct in the EU of clinical trials on medicinal products for human use. ENTR/6416/01, July 2002

- Investigators brochure (+ updates) or SmPC
- Protocol and amendments (signed)
- Information sheet and consent form (+ updates)
- Financial aspects
- Insurance statements
- Signed agreements between parties
- EC opinion and composition
- MRHA authorisation
- Investigators CVs
- Medical and laboratory tests, including normal ranges
- Medicine labels
- Instructions for medicine use
- Shipping records
- Certificates of analysis
- Decoding procedures
- Master randomisation list
- Monitoring reports (pre-trial, initiation, close-out etc)
- List of persons responsibilities delegated to (+ updates)
- CRFs and corrections
- SAE notifications from investigators and to EC and MRHA
- EC/MRHA annual reports and final reports
- Subject screening log
- Subject identification code list
- Subject enrolment log
- IMP accountability at site
- Record of retained tissues
- Documentation of IMP destruction
- Completed subject identification code list
- Audit certificate
- Clinical study report
Would it be feasible to limit the number of centers by performing the trial in selected large countries only?
EURAMOS target population 606.57 million
ca. 8.7% of world population
78% of recruitment

75.4% of population

24.6% of population

22% of recruitment

USA: 974
GER: 422
UK: 291
CDN: 78
AUS: 27
NL: 96
BE: 48
CZ: 9
HUN: 24
SE: 46
A: 25
CH: 37
DK: 26
FIN: 3
NOR: 40
NZL: 14
IRE: 4
Centers (n=328)

Australia 6
Austria 5
Belgium 6
Canada 14
Czech Rep. 2
Denmark 2
Finland 1
Germany 84
Hungary 2
Ireland 1
Netherlands 4
New Zeald. 3
Norway 3
Sweden 6
Switzerland 8
UK 24
USA 152

USA incl. Puerto Rico. 4 COG centers in 3 other countries
75.4% of population
79.3% of centers
Limiting the trial to a few large countries would reduce national regulatory and ethical submissions, but would not reduce the number of centers considerably.
Would it be feasible to perform such trials in selected large centers only?
EURAMOS Patients per center

Median  5
Min    1
Max  90
Mean  6.6

328 centers
2,169 patients
EOI Patients per center

Median 9
Min 1
Max 90
Mean 12.5

35 centers
439 patients
SSG Patients per center

Median 7.5
Min 2
Max 29
Mean 9.6

12 centers
115 patients
COG Patients per center

Median 5
Min 1
Max 24
Mean 6.1

183 centers
1,108 patients
COSS Patients per center

Median 3
Min 1
Max 35
Mean 5.2

98 centers
506 patients
EURAMOS  Patients per center per year

<table>
<thead>
<tr>
<th>Range</th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5</td>
<td>3</td>
<td>0.9%</td>
</tr>
<tr>
<td>4-4.99</td>
<td>2</td>
<td>0.6%</td>
</tr>
<tr>
<td>3-3.99</td>
<td>14</td>
<td>4.3%</td>
</tr>
<tr>
<td>2-2.99</td>
<td>34</td>
<td>10.4%</td>
</tr>
<tr>
<td>1-1.99</td>
<td>90</td>
<td>27.4%</td>
</tr>
<tr>
<td>&lt;1</td>
<td>185</td>
<td>56.4%</td>
</tr>
</tbody>
</table>

54 (16.4%) 1 patient total
Patients per center per year

(based on total 6 year EURAMOS recruitment period)

<table>
<thead>
<tr>
<th>Size</th>
<th>Centers</th>
<th>5 &amp; more</th>
<th>4 to 4.99</th>
<th>3 to 3.99</th>
<th>2 to 2.99</th>
<th>1 to 1.99</th>
<th>less than 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;large&quot;</td>
<td>n=53</td>
<td>3</td>
<td>2</td>
<td>14</td>
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</tr>
<tr>
<td>small</td>
<td>n=275</td>
<td>90</td>
<td>185</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

16.2% of centers

83.8% of centers
EURAMOS Patients per center

0.9% of centers
8.1% of patients

<table>
<thead>
<tr>
<th>Pts/year</th>
<th>centers</th>
<th>pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5</td>
<td>3</td>
<td>175</td>
</tr>
</tbody>
</table>

(0.9%) (8.1%)
1.5% of centers
10.5% of patients

<table>
<thead>
<tr>
<th>Pts/year</th>
<th>centers</th>
<th>pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-4.99</td>
<td>2</td>
<td>53 (2.4%)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>3</td>
<td>175 (8.1%)</td>
</tr>
</tbody>
</table>
EURAMOS Patients per center

5.8% of centers
23.4% of patients

<table>
<thead>
<tr>
<th>Pts/year</th>
<th>centers</th>
<th>pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-3.99</td>
<td>14</td>
<td>280 (12.9%)</td>
</tr>
<tr>
<td>4-4.99</td>
<td>2</td>
<td>53 (2.4%)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>3</td>
<td>175 (8.1%)</td>
</tr>
</tbody>
</table>
EURAMOS Patients per center

16.2% of centers
45.8% of patients

<table>
<thead>
<tr>
<th>Pts/year</th>
<th>centers</th>
<th>pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-2.99</td>
<td>34</td>
<td>485 (22.3%)</td>
</tr>
<tr>
<td>3-3.99</td>
<td>14</td>
<td>280 (12.9%)</td>
</tr>
<tr>
<td>4-4.99</td>
<td>2</td>
<td>53 (2.4%)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>3</td>
<td>175 (8.1%)</td>
</tr>
</tbody>
</table>
**EURAMOS**

43.6% of centers
77.5% of patients

<table>
<thead>
<tr>
<th>Pts/year</th>
<th>centers</th>
<th>pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1.99</td>
<td>90</td>
<td>688</td>
</tr>
<tr>
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<td>34</td>
<td>485</td>
</tr>
<tr>
<td>3-3.99</td>
<td>14</td>
<td>280</td>
</tr>
<tr>
<td>4-4.99</td>
<td>2</td>
<td>53</td>
</tr>
<tr>
<td>&gt;5</td>
<td>3</td>
<td>175</td>
</tr>
</tbody>
</table>
EURAMOS Patients per center

100% of centers
100% of patients

<table>
<thead>
<tr>
<th>Pts/year</th>
<th>centers</th>
<th>pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>185</td>
<td>487</td>
</tr>
<tr>
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<td>90</td>
<td>688</td>
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<td>34</td>
<td>485</td>
</tr>
<tr>
<td>3-3.99</td>
<td>14</td>
<td>280</td>
</tr>
<tr>
<td>4-4.99</td>
<td>2</td>
<td>53</td>
</tr>
<tr>
<td>&gt;5</td>
<td>3</td>
<td>175</td>
</tr>
</tbody>
</table>
Patients per center per year

(based on total 6 year EURAMOS recruitment period)

- 53 centers, 993 patients (large)
- 275 centers, 1,175 patients (small)

<table>
<thead>
<tr>
<th>Patients per center per year</th>
<th>1 to 1,99</th>
<th>less than 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 &amp; more</td>
<td>175</td>
<td>688</td>
</tr>
<tr>
<td>4 to 4.99</td>
<td>53</td>
<td>487</td>
</tr>
<tr>
<td>3 to 3.99</td>
<td>280</td>
<td>485</td>
</tr>
<tr>
<td>2 to 2.99</td>
<td>485</td>
<td></td>
</tr>
</tbody>
</table>

- 16.2% of centers, 45.8% of patients (large)
- 83.8% of centers, 54.2% of patients (small)
More than half of all patients are recruited by (very) low volume contributors
Are the high volume recruiters concentrated in a few countries?
<table>
<thead>
<tr>
<th>Country</th>
<th>Centers &gt;=2 patients/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>0</td>
</tr>
<tr>
<td>Austria</td>
<td>0</td>
</tr>
<tr>
<td>Belgium</td>
<td>2</td>
</tr>
<tr>
<td>Canada</td>
<td>2</td>
</tr>
<tr>
<td>Czech Rep.</td>
<td>0</td>
</tr>
<tr>
<td>Denmark</td>
<td>1</td>
</tr>
<tr>
<td>Finland</td>
<td>0</td>
</tr>
<tr>
<td>Germany</td>
<td>9</td>
</tr>
<tr>
<td>Hungary</td>
<td>1</td>
</tr>
<tr>
<td>Ireland</td>
<td>0</td>
</tr>
<tr>
<td>Netherlands</td>
<td>3</td>
</tr>
<tr>
<td>New Zealand</td>
<td>0</td>
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<tr>
<td>Norway</td>
<td>1</td>
</tr>
<tr>
<td>Sweden</td>
<td>2</td>
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<tr>
<td>Switzerland</td>
<td>0</td>
</tr>
<tr>
<td>UK</td>
<td>8</td>
</tr>
<tr>
<td>USA</td>
<td>24</td>
</tr>
</tbody>
</table>

Based on total 6 year recruitment period (n=53)

10/17 countries
Centers >=2 patients/year

Based on national trial opening (n=64)

<table>
<thead>
<tr>
<th>Country</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>0</td>
</tr>
<tr>
<td>Austria</td>
<td>1</td>
</tr>
<tr>
<td>Belgium</td>
<td>2</td>
</tr>
<tr>
<td>Canada</td>
<td>2</td>
</tr>
<tr>
<td>Czech Rep.</td>
<td>1</td>
</tr>
<tr>
<td>Denmark</td>
<td>1</td>
</tr>
<tr>
<td>Finland</td>
<td>0</td>
</tr>
<tr>
<td>Germany</td>
<td>9</td>
</tr>
<tr>
<td>Hungary</td>
<td>1</td>
</tr>
<tr>
<td>Ireland</td>
<td>1</td>
</tr>
<tr>
<td>Netherlands</td>
<td>4</td>
</tr>
<tr>
<td>New Zealand</td>
<td>1</td>
</tr>
<tr>
<td>Norway</td>
<td>1</td>
</tr>
<tr>
<td>Sweden</td>
<td>2</td>
</tr>
<tr>
<td>Switzerland</td>
<td>0</td>
</tr>
<tr>
<td>UK</td>
<td>8</td>
</tr>
<tr>
<td>USA</td>
<td>30</td>
</tr>
</tbody>
</table>

14/17 countries
Centers $\geq 2$ patients/year

Based on national trial opening (n=64)

Top 10 7/17 countries
Top 20 9/17 countries
Top 50 14/17 countries
Is there no way to concentrate patients?
Australia
Austria
Belgium
Canada
Czech Rep.
Denmark
Finland
Germany
Hungary
Ireland
Netherlands
New Zealnd.
Norway
Sweden
Switzerland
UK
USA

Resident Royals
Resident Royalty

**No**
11 countries, 287 centers

- **Median**: 4 pts/center
- **Min**: 1
- **Max**: 50
- **Mean**: 5.98
  +/- 5.88

**Yes**
6 countries, 41 centers

- **Median**: 8 pts/center
- **Min**: 1
- **Max**: 90
- **Mean**: 11.00
  +/- 14.10
Resident Royalty

No
11 countries, 287 centers
Median 4 pts/center
Min 1
Max 50
Mean 5.98 +/- 5.88

Yes
6 countries, 41 centers
Median 8 pts/center
Min 1
Max 90
Mean 11.00 +/- 14.10

p < 0.00001 (t-test)
Unless major political changes occur:

**Considerable fragmentation of care needs to be taken into account when planning, initiating, running, and regulating large scale clinical trials in rare cancers.**
The EURAMOS investigators thank ESF and its Member Organisations for their support.

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Klinikum Stuttgart – Medizin fürs Leben

Danke für Ihre Aufmerksamkeit!