Monitoring of Patient Recruitment in Surgical Trials

Inga Rossion, Markus K. Diener, C. M Seiler

Study Center of the German Surgical Society
Dept. of General, Visceral and Transplantation Surgery
University Hospital, Heidelberg, Germany

Federal Ministry
of Education
and Research

Background

Facts:

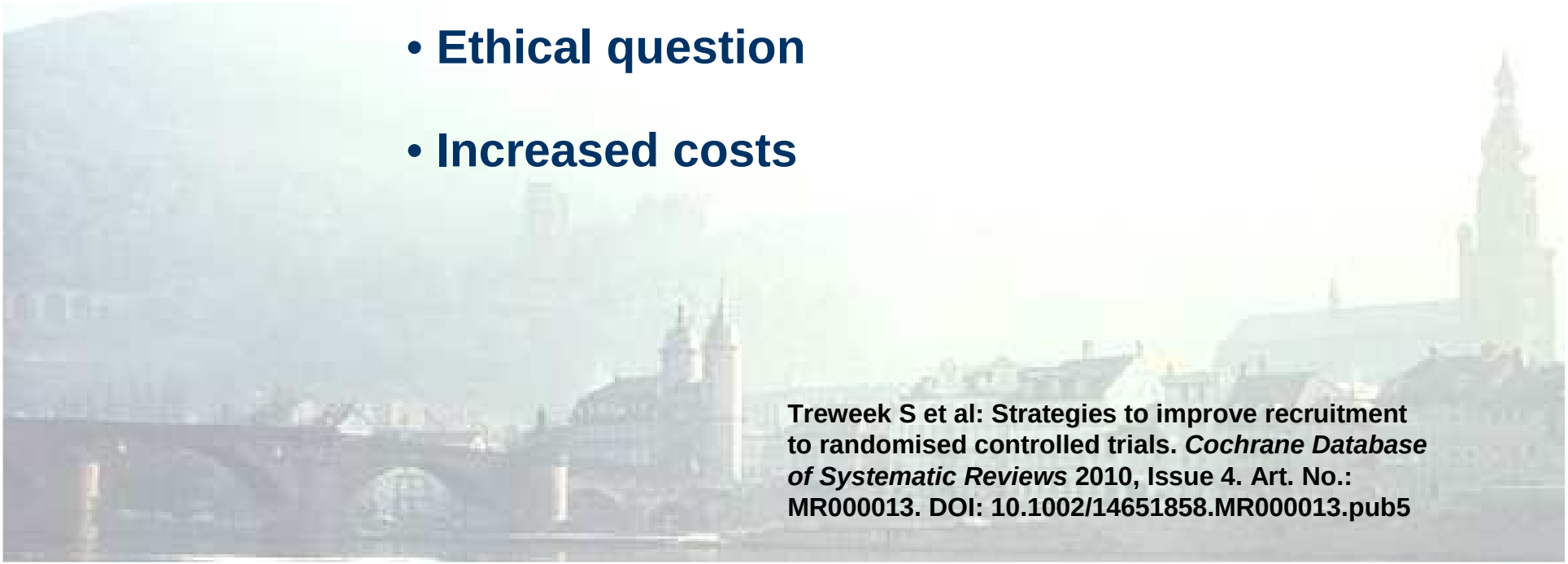
114 trials, 1994-2002

- **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 *Trials* 2006, 7:9 doi:10.1186/1745-6215-7-9

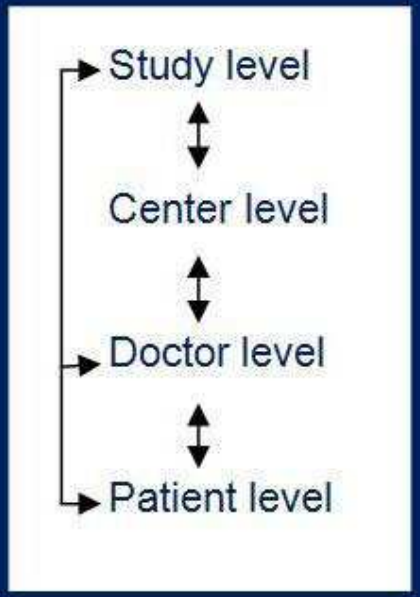
Consequences of poor recruitment

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



Treweek S et al: Strategies to improve recruitment to randomised controlled trials. *Cochrane Database of Systematic Reviews* 2010, Issue 4. Art. No.: MR000013. DOI: 10.1002/14651858.MR000013.pub5

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?

Oude Rengerink et al.
BMC Medical Research Methodology 2010, 10:85
http://www.biomedcentral.com/1471-2288/10/85

Recruitment in surgical trials
Levels of influence

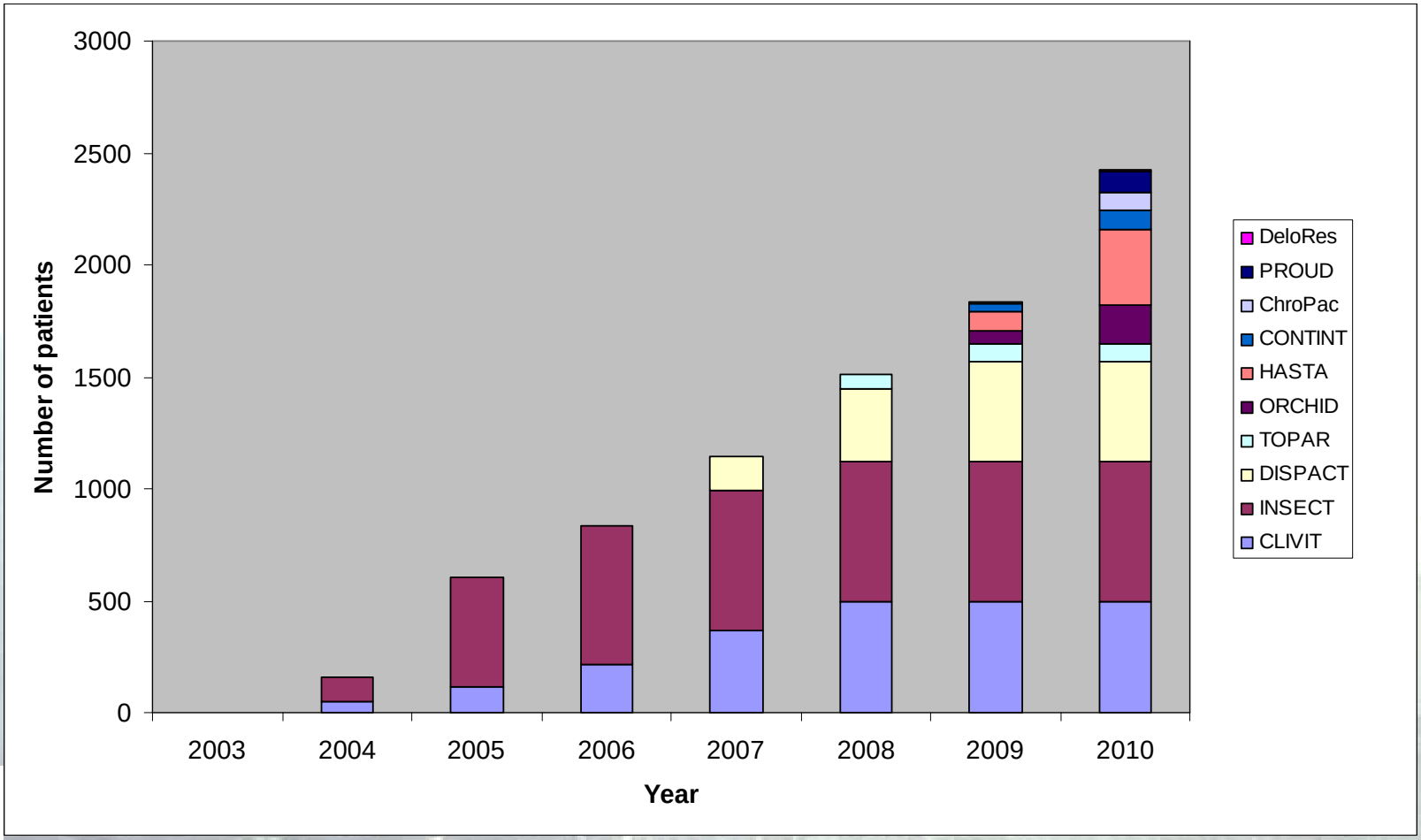
Patient :	**Less influence compared to drug trials.** **Important: patient informed consent.**
Surgeon:	**Surgical skill and experience are essential,** **Convictions may have large influence.** **Training issue.**
Center:	**Different surgical (house) standards may interfere with trial procedures.** **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

Seiler CM, Diener MK, Rahbari N, Bauer H, Rothmund M, Büchler MW. Coordinating a national clinical trials center: the German experience. Surgery. 2009 Jun;145(6):590-7

Recruited patients in SDGC trials 2003 - 2010



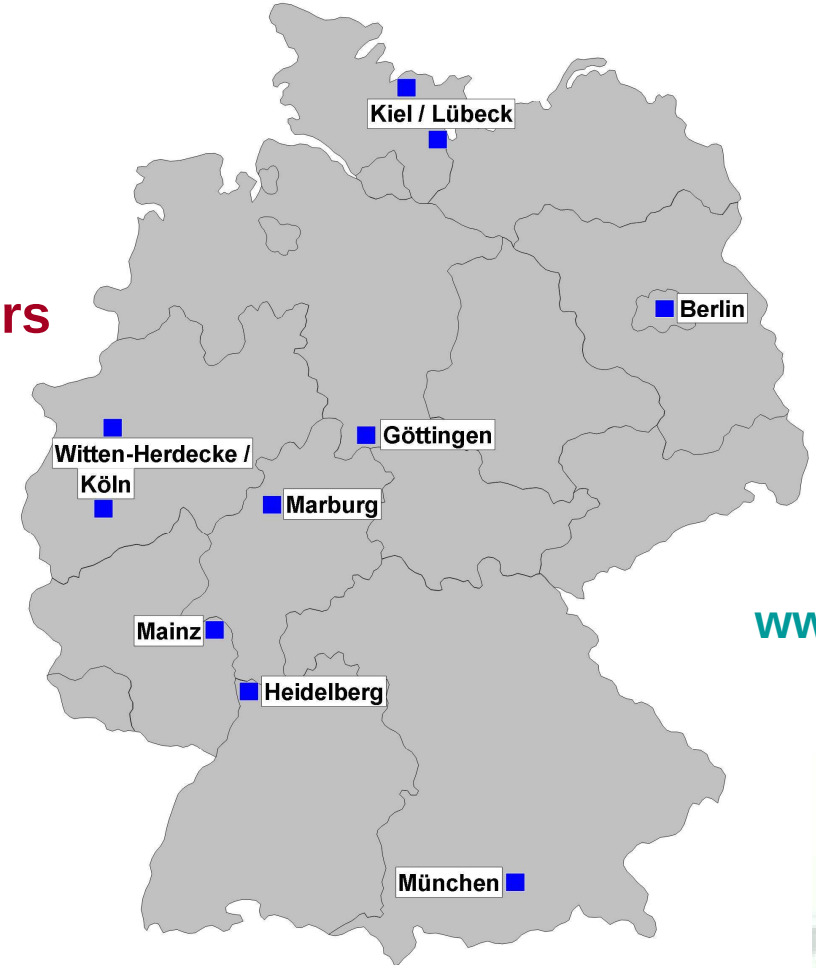
Balance of activities*

- **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



www.chir-net.de

Federal Ministry of Education and Research

Rahbari NN, Diener MK, Fischer L, Wente MN, Kienle P, Büchler MW, Seiler CM. A concept for trial institutions focussing on randomised controlled trials in surgery. *Trials*. 2008 Jan 24;9:3.

Projected vs. real time

ChroPac trial: original schedule (2008)			Adapted (5/2010)	
Milestones	**Quarter**	**Year**	**Quarter**	**Year**
First patient in	April	2009	**June**	**2009**
Last patient in	**I**	**2011**	**I**	**2012**
Patient follow-up	II	2013	**I**	**2014**
Data base closure	II	2013	**II**	**2014**
Data analysis	III	2013	**III**	**2014**
Biostatistical report	IV	2013	**IV**	**2014**
Publication	IV	2013	**IV**	**2014**

1 year behind schedule

Trials 2010, 1:47
doi:10.1186/1745-6215-11-47

Commitment of centers

ChroPac trial

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

*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

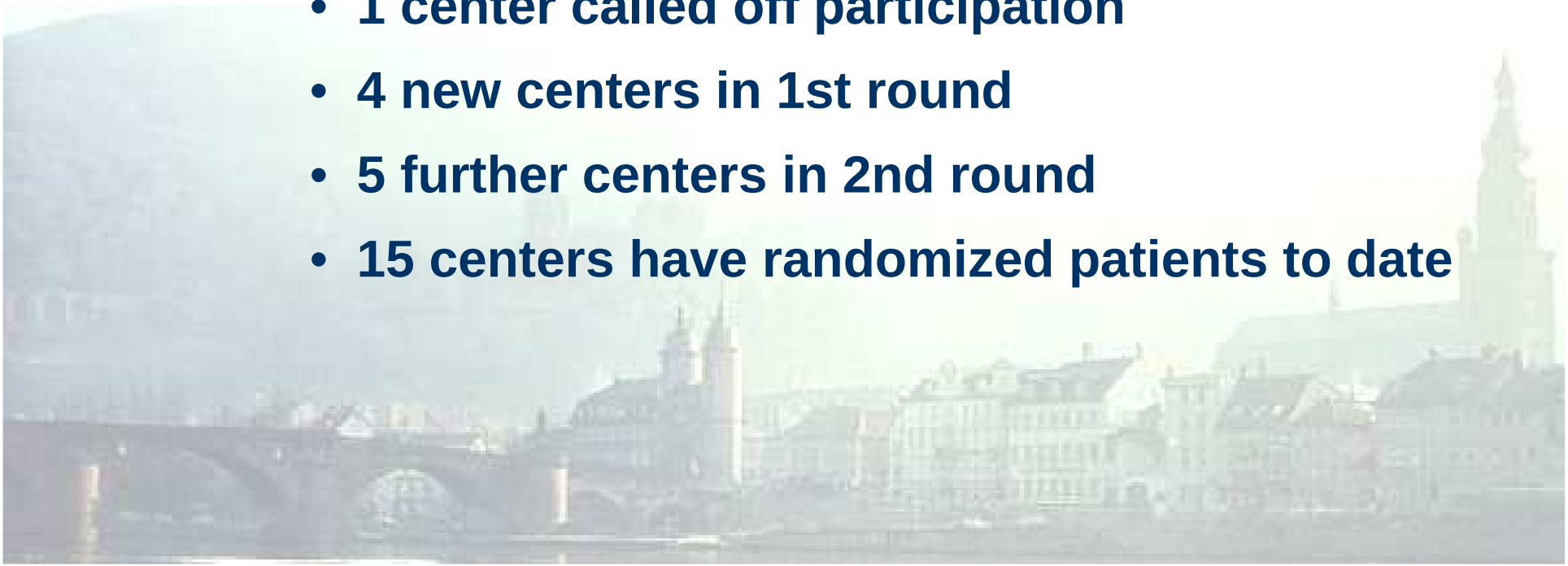
Specification of inclusion criterion communicated in Newsletter 3 and by monitors

(Amendment is necessary, if eligibility criteria are changed.)

Measures taken to improve recruitment

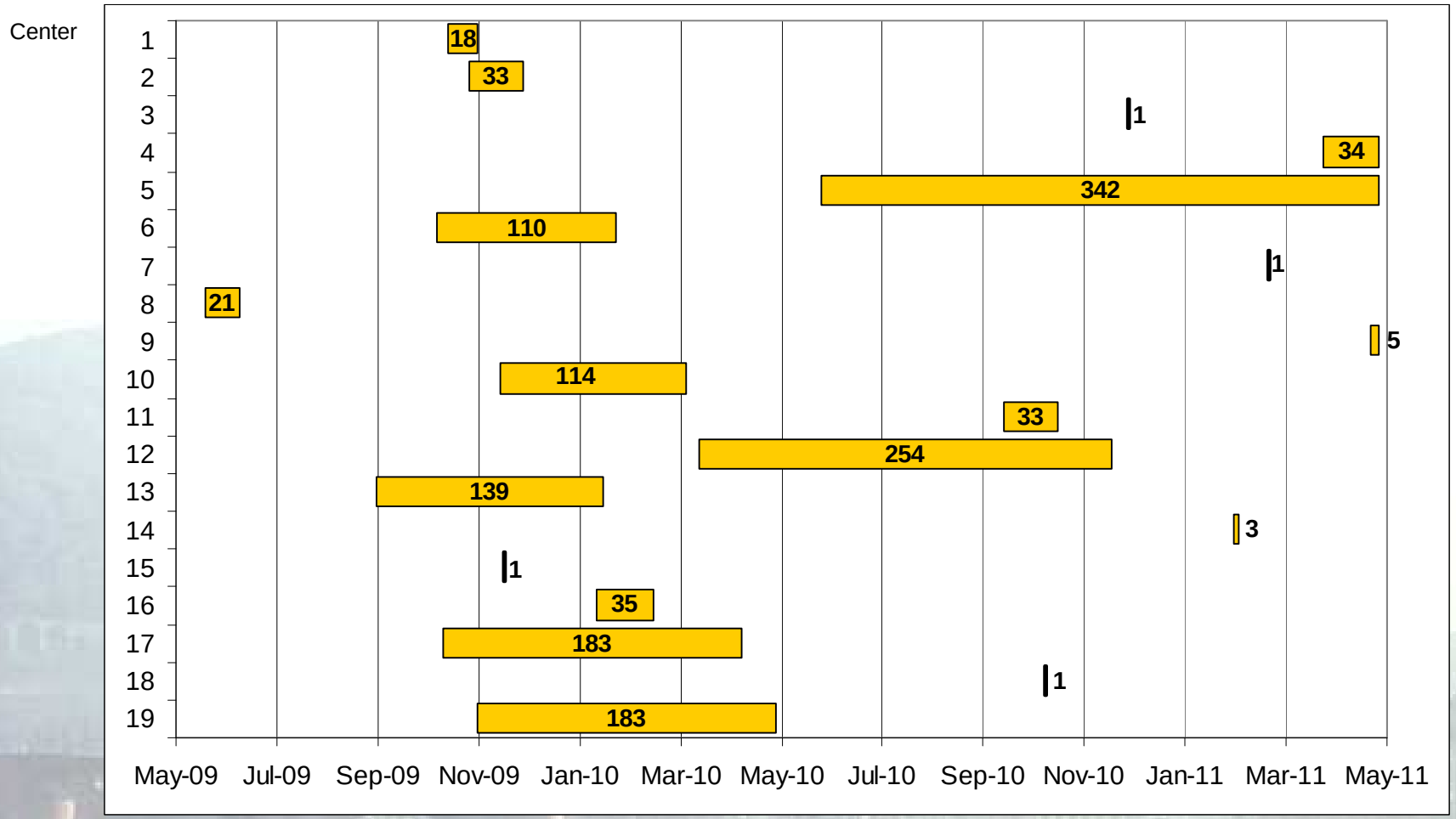
New participating centers

- 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

Results: improved recruitment

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

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

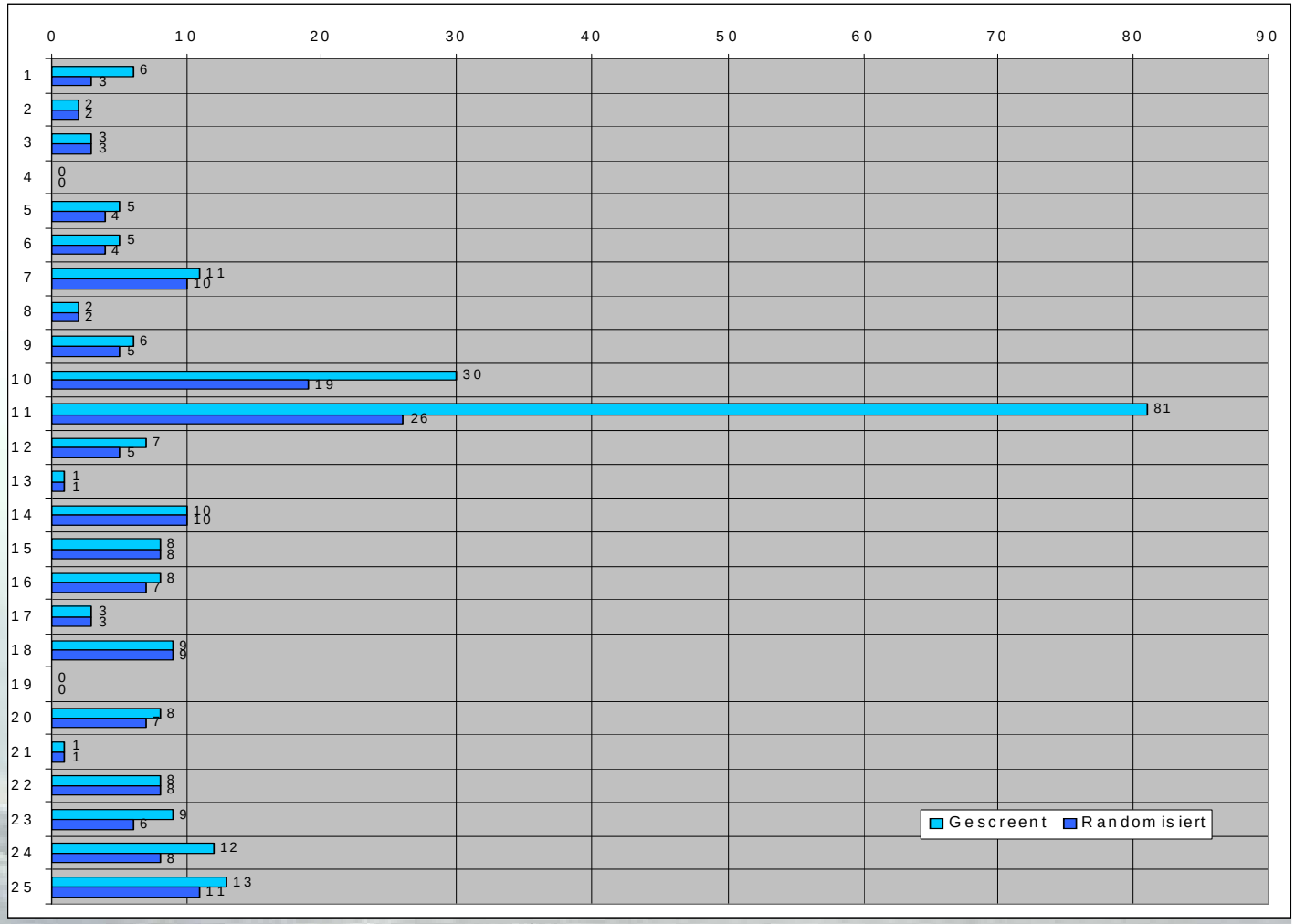
Recruitment potential

HASTA trial: Patients screened – randomized

Have all potential patients been identified?

Screened?

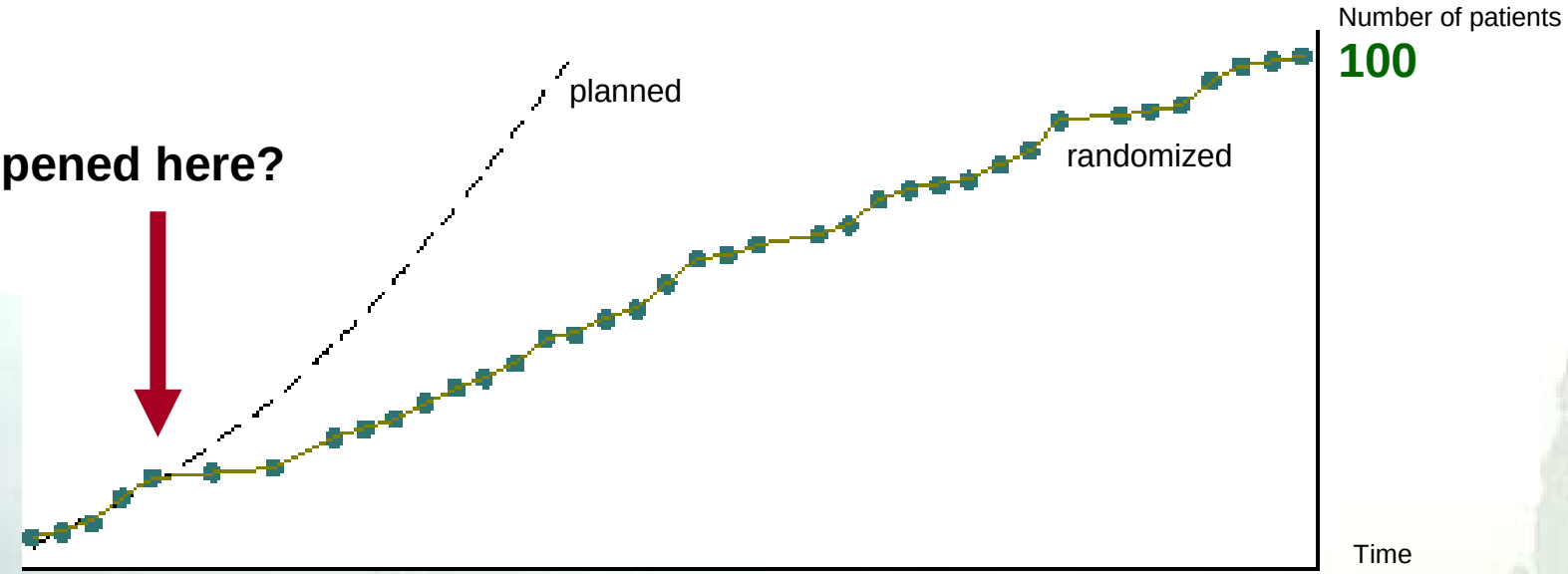
Can the randomization rate be improved?



Trials 2011, 12:34
doi:10.1186/
1745-6215-12-34

Good start and then …

TOPAR-pilot trial: Planned vs. real course



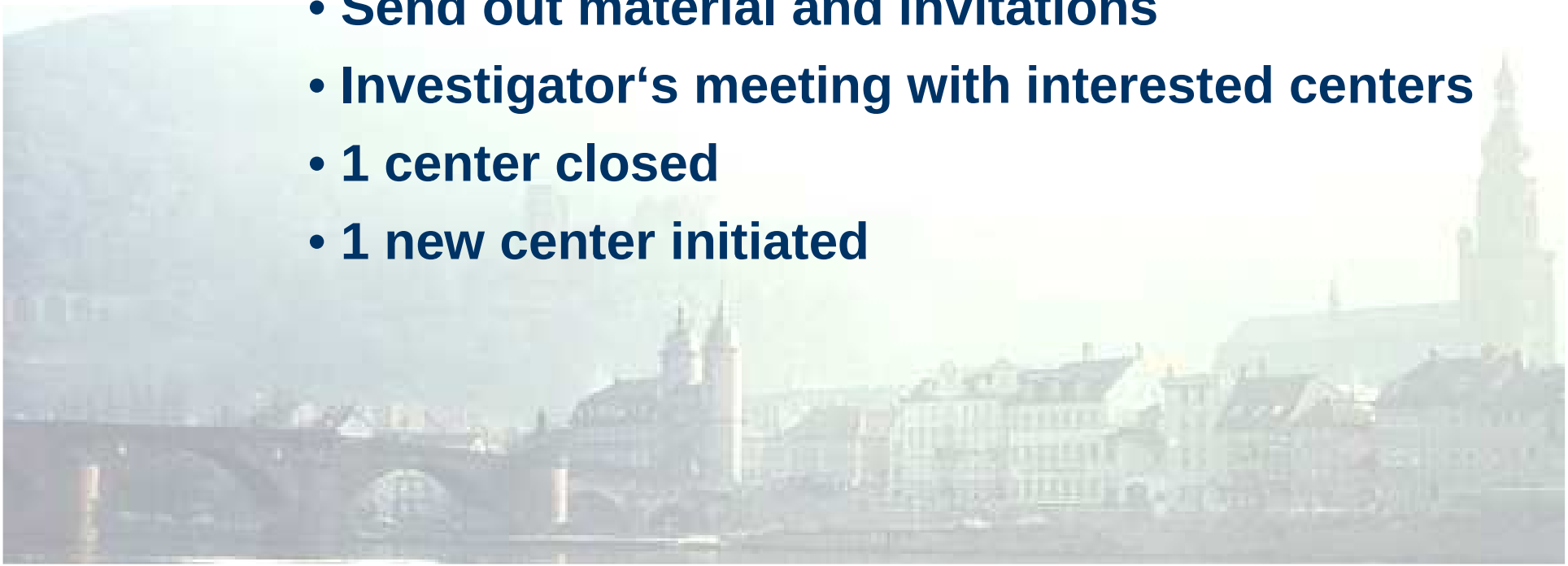
Market access of new drug (Cinacalcet) reduced number patients undergoing surgical treatment.

Recruitment time was prolonged from 18 to 43 months.

Trials **2007, 8:22**
doi:10.1186/1745-6215-8-22

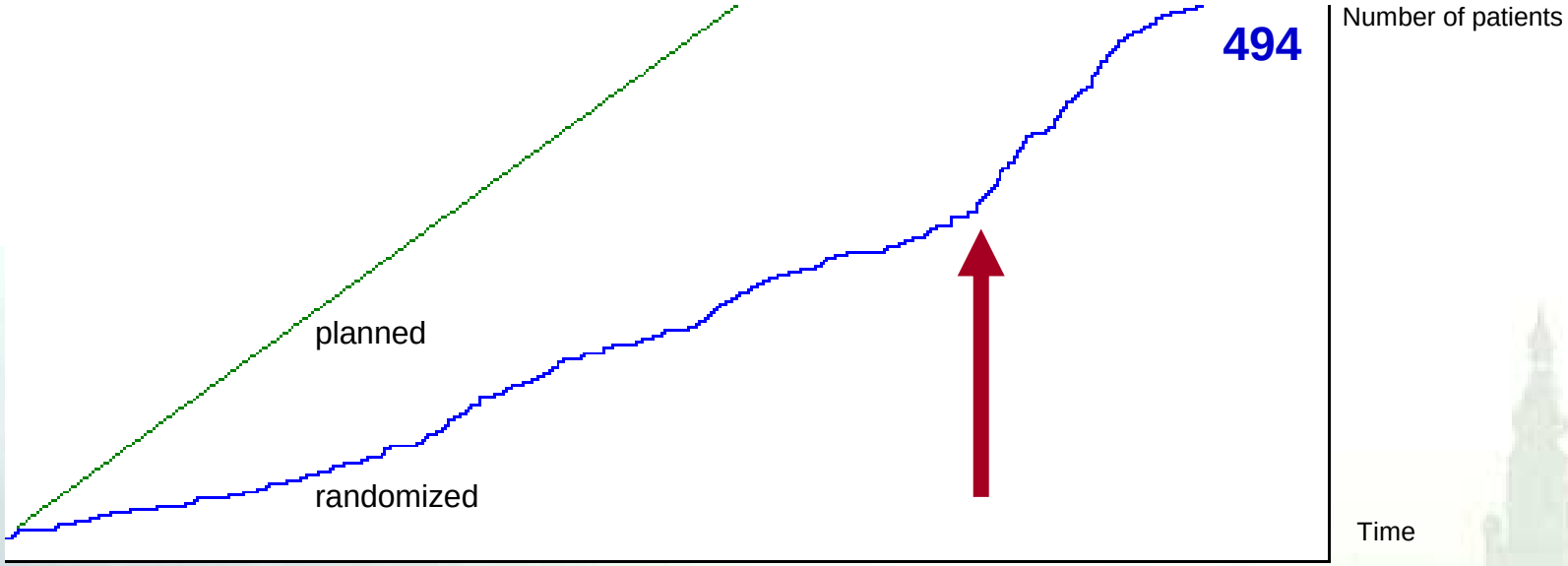
TOPAR-pilot: Actions taken

- 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

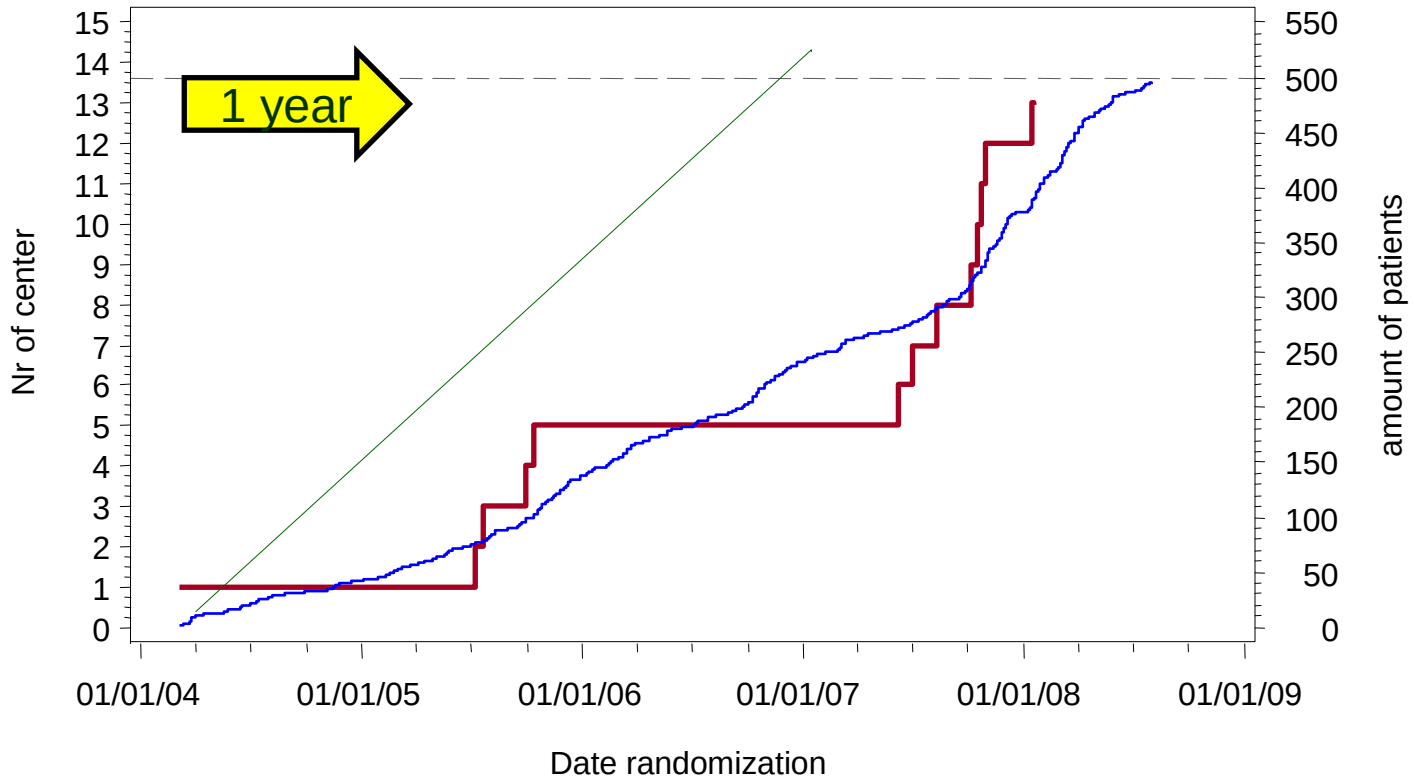
CLIVIT trial: Planned vs. real course



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

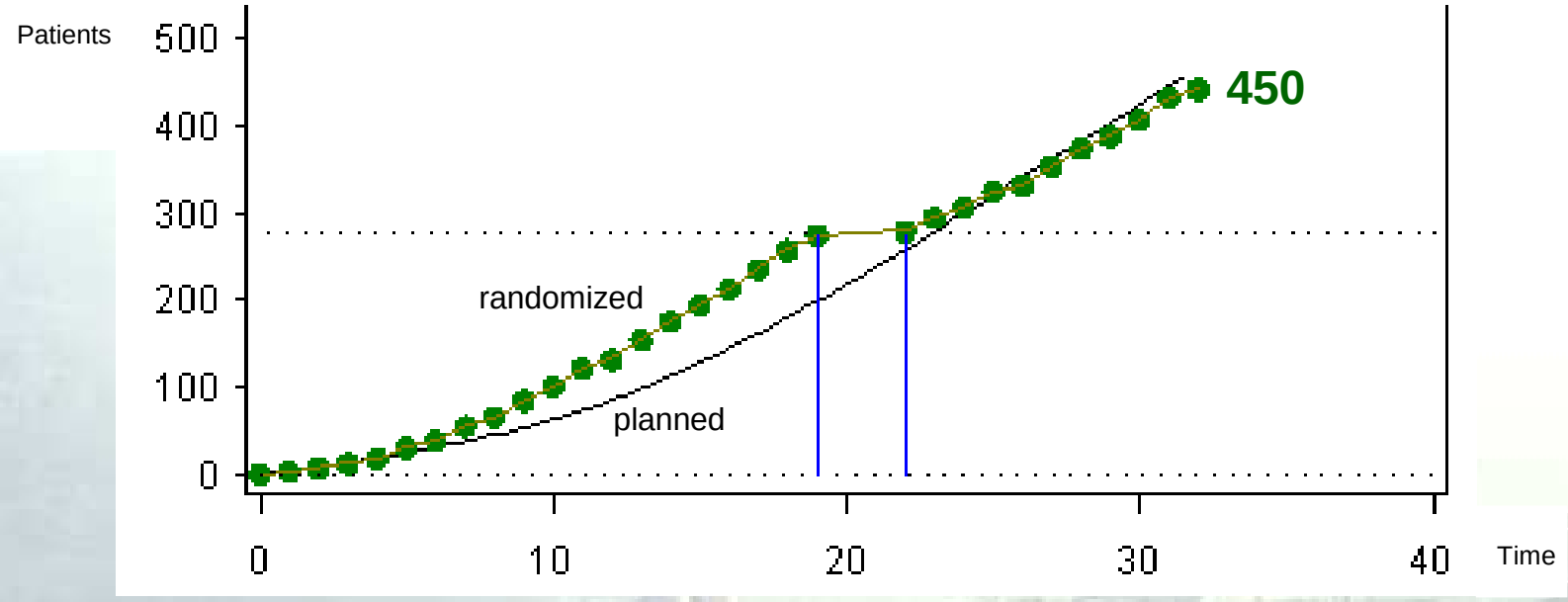
CLIVIT - Recruitment



4 ½ years of recruitment instead of 3 years

Recruitment ahead of schedule

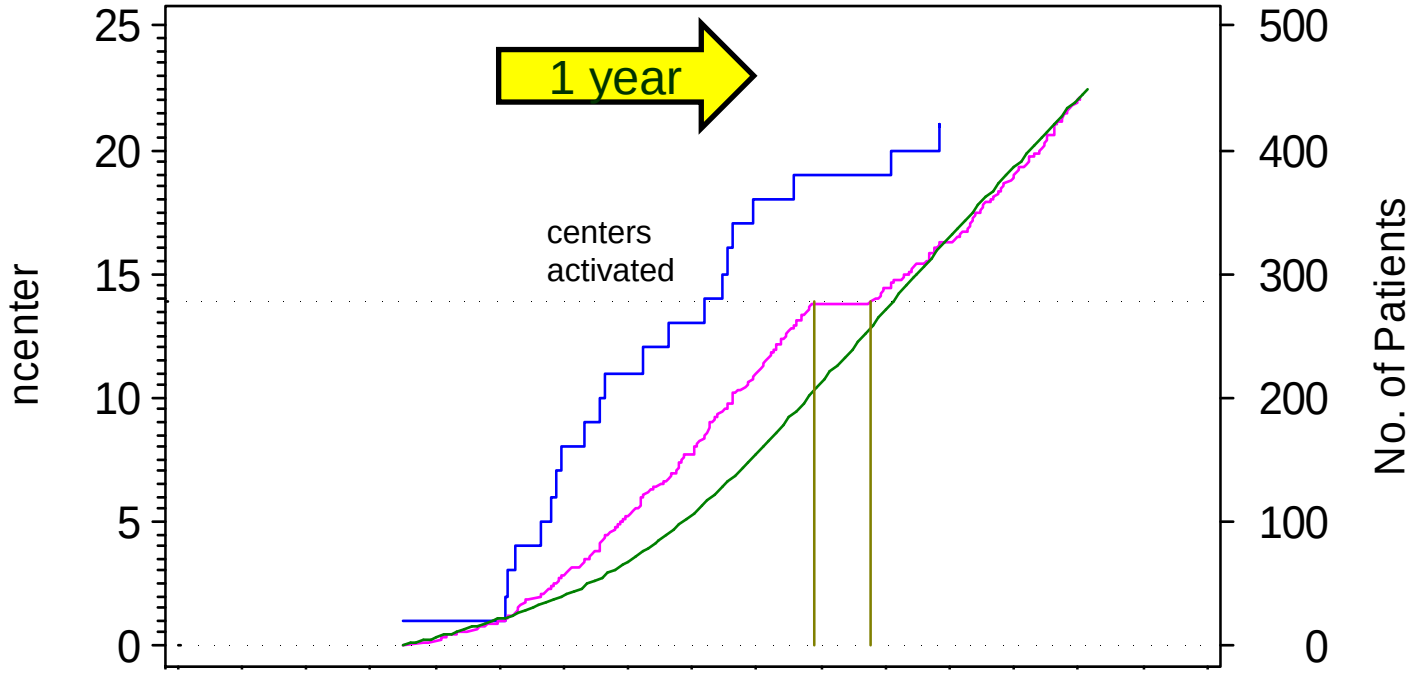
DISPACT trial: planned vs. real course



Clin Trials 2008 5: 534
DOI: 10.1177/1740774508096140

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

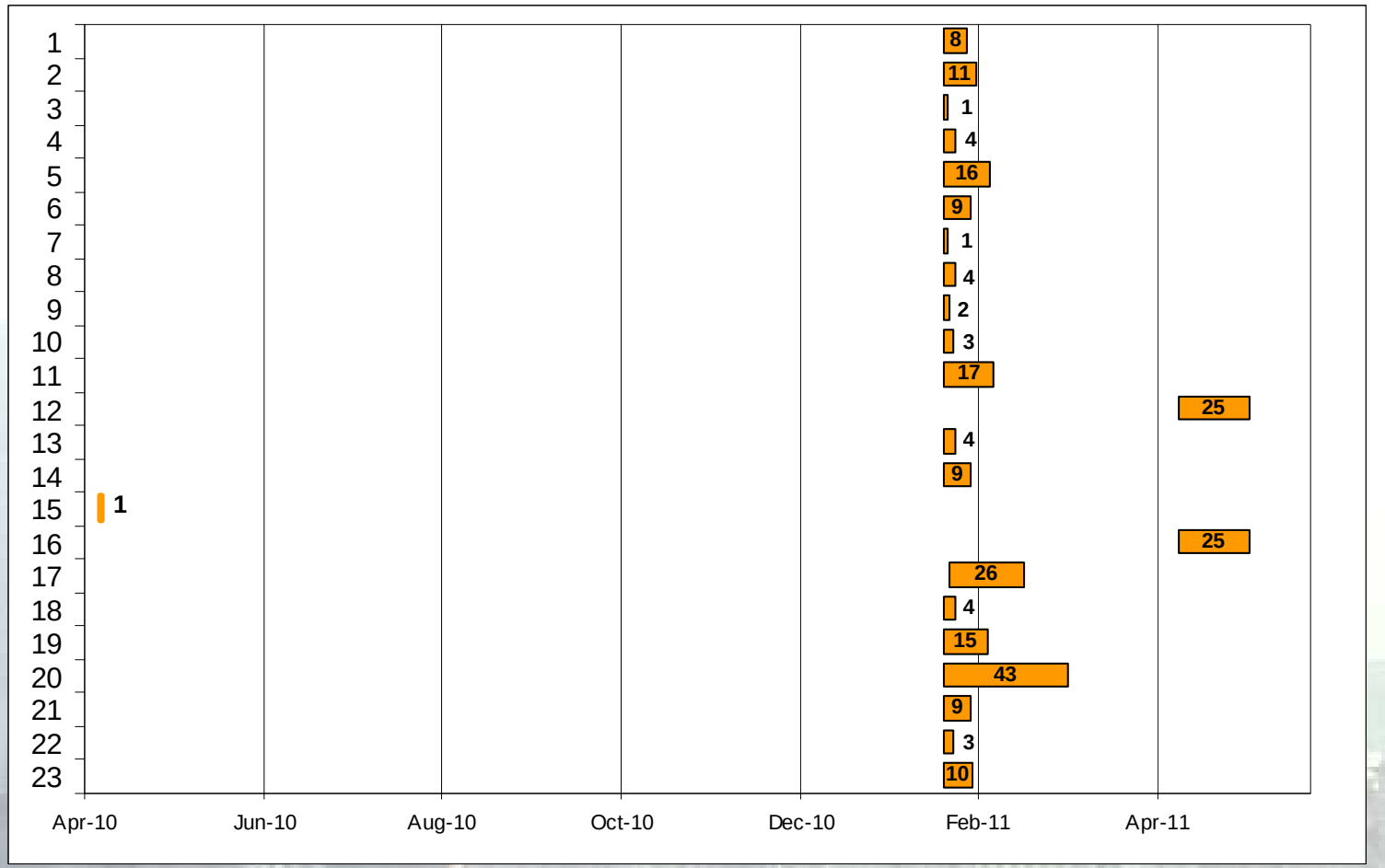
Obstacles: Interim analysis



- **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

www.sdgc.de