International trials of the GCLLSG: regulatory requirements and corrective actions

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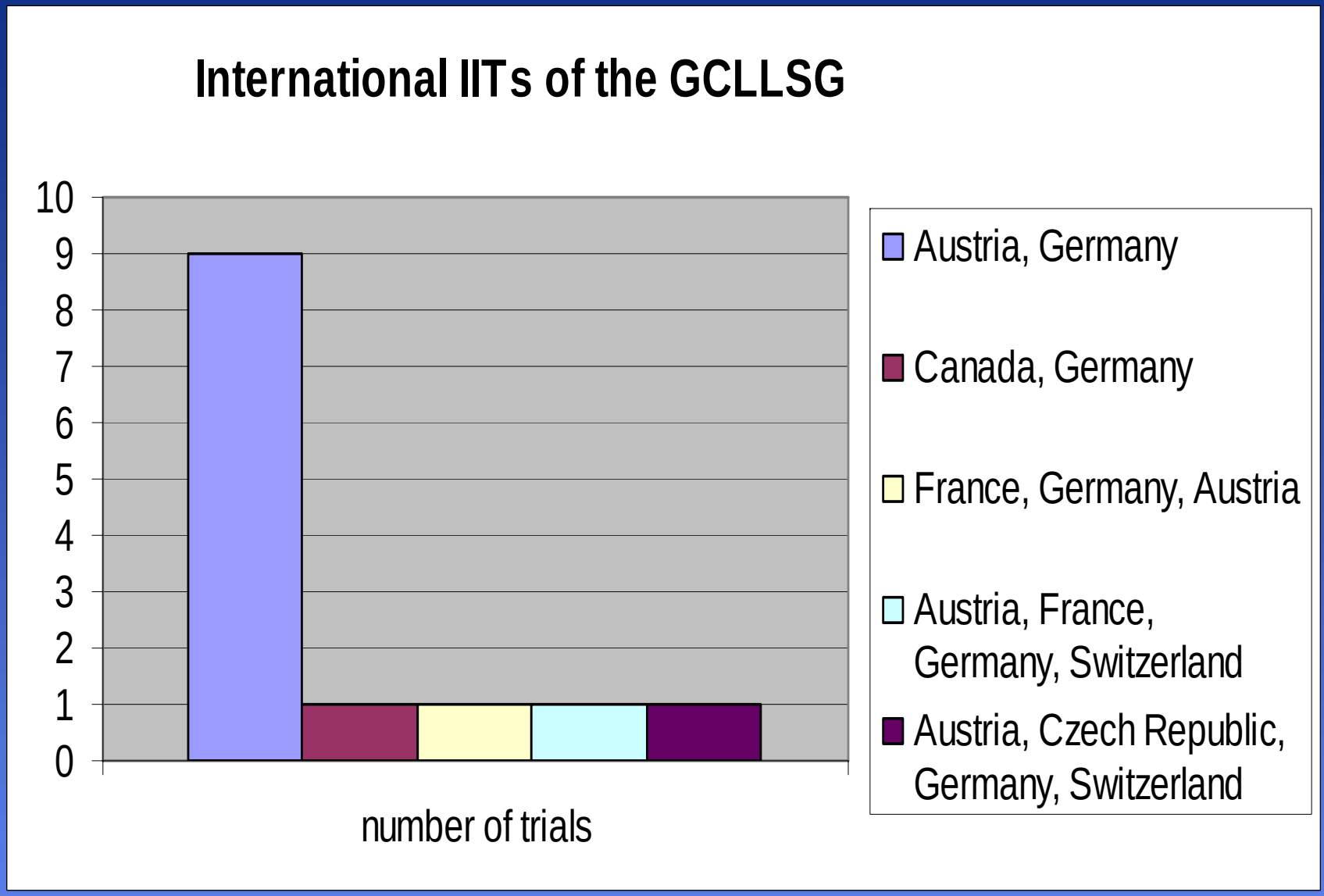
5th Symposium of ELN, 28.01.2008

German CLL Study Group: Background

The German CLL Study Group (GCLLSG) was founded in 1996 to improve diagnostics and treatment of CLL

- **26 Investigator Initiated Trials since 1996**
- **1 pharma-sponsored registration trial in close collaboration with GCLLSG**
- **350 cooperating sites**
- **3600 registered CLL patients**

International GCLLSG Trials



Improvement Process

Due to non compliance-issues concerning trials conducted before 12th amendment to drug law

- **GCLLSG asked for a lawyers opinion**
- **Local authorities gave advice to GCLLSG**
- **GCLLSG was audited by pharma company**
- **GCLLSG set up status report "regulatory inconsistency„ and action plan**

<u>actions:</u>

- **GCLLSG made for outstanding submissions**
- **GCLLSG personnel was trained on GCP-Guidelines, trial set-up and trial conduct (at least 2 times per year ever since)**
- **Additional staff was hired to cope with increased administrative work**

New processes were implemented

- **Clear definition of *roles and responsibilities*, preparation of flow charts**
- **Developing *project plan with project time lines***
- ***Site selection* as well as preparation and conclusion of contracts**
- **Double data entry and *data cleaning prior to medical review***
- **preparation of *monitoring plan* and performance of *onsite-monitoring* by CRO**
- **SAE-Management including *SAE collection*, Medical case reviews, *evaluation, reconciliation* and reporting**
- **Design of Standard Operation Procedures and working according the *SOPs***

Changes in trial conduct: CLL4 vs. CLL10

Corrective actions had an effect on GCLLSG trial conduct. Quality was improved but administrative work and costs were increased.

CLL4:

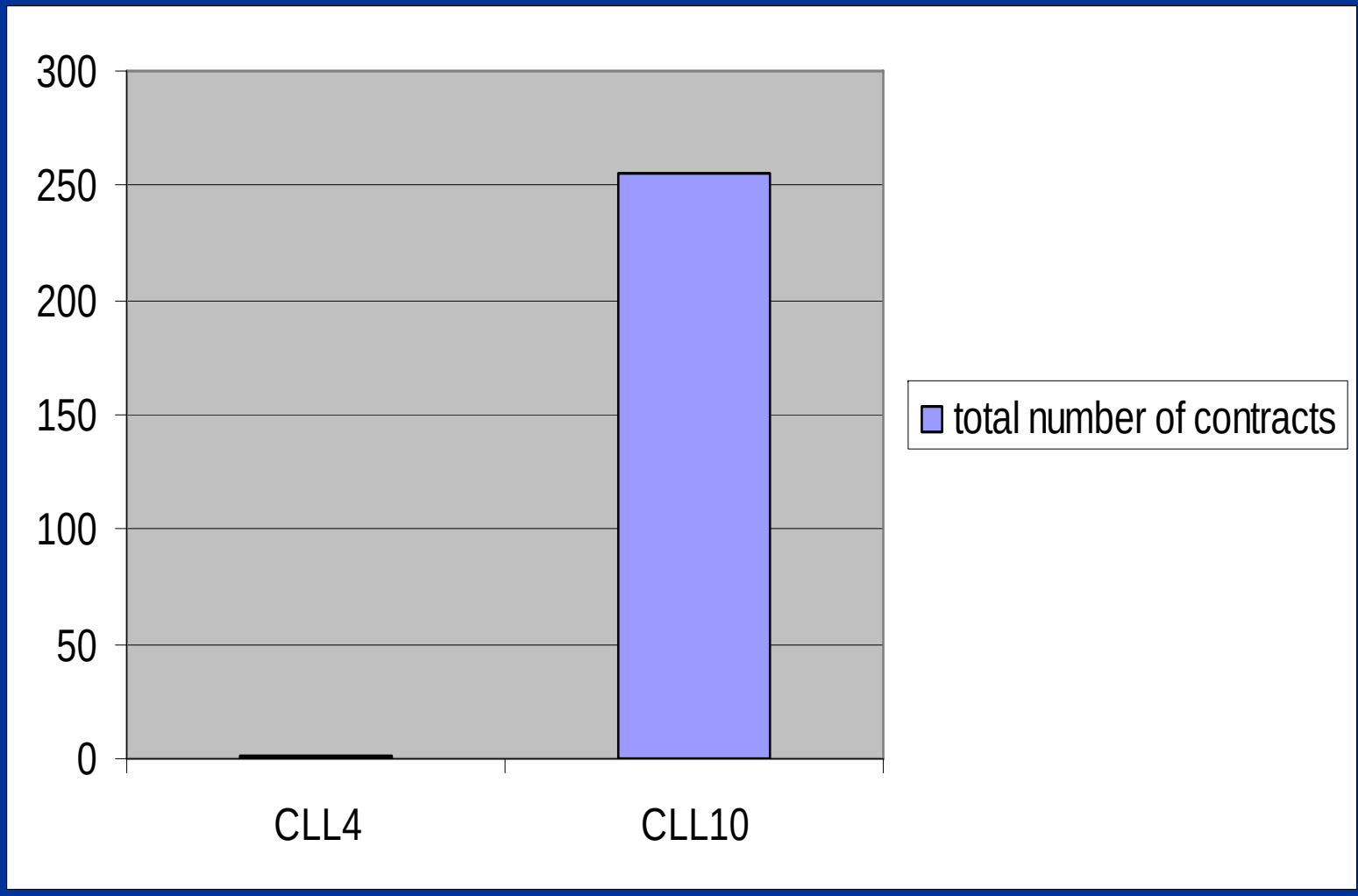
started in 1999 - before 12th amendment to drug law became effective

CLL10:

Will start in April 2008- after 12th amendment to drug law became effective

CLL4 vs. CLL10: size

CLL4 vs. CLL10: total number of contracts



CLL4 vs CLL10: Contracts

investigator contracts	0 (letter of intent)	130
pharma contracts	1	2
contracts with CRO	0	3
contracts with central labs	0	4
pharmacy contracts	0	114
other contracts	0	2

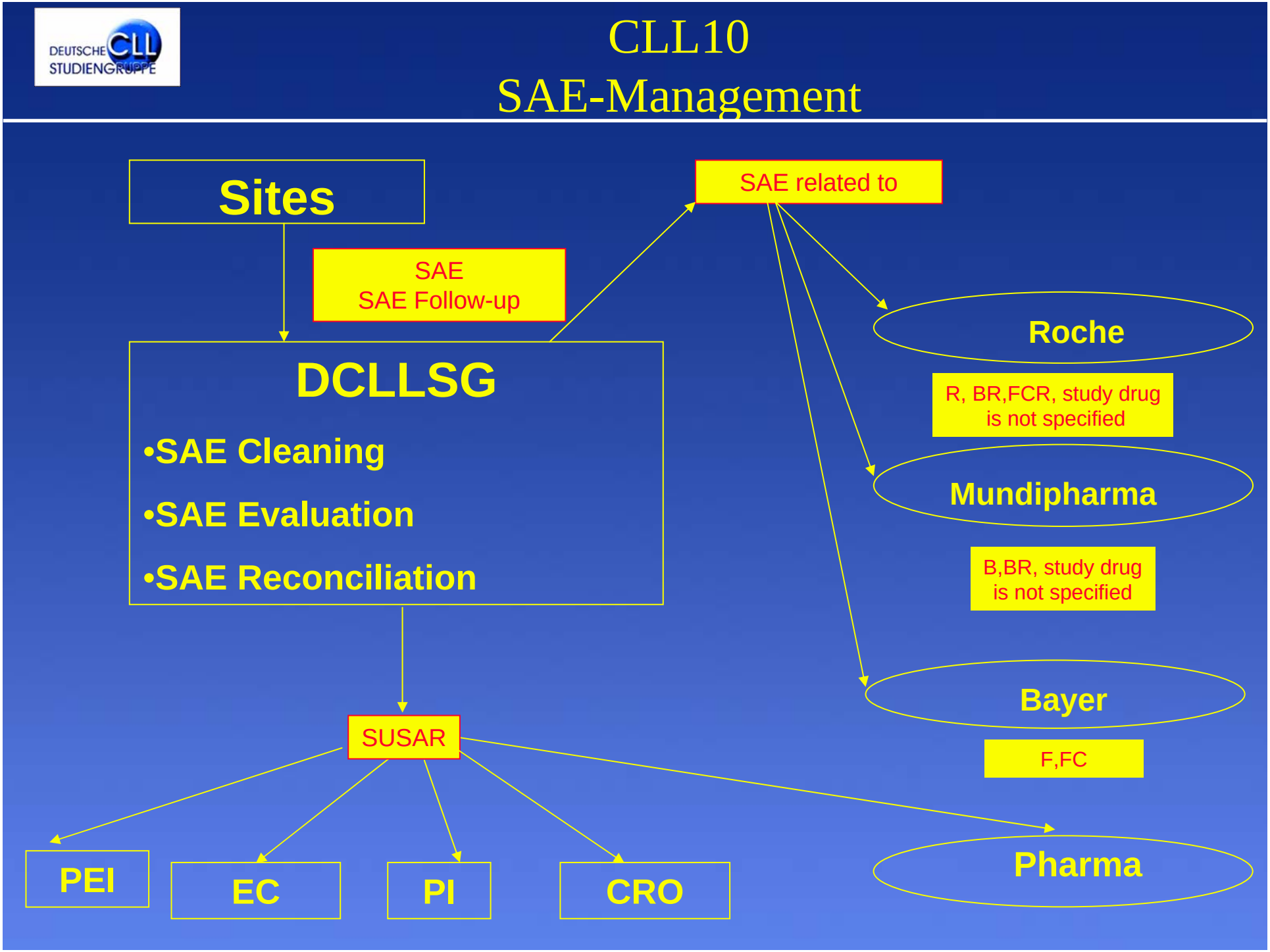
Contracts: current problems

- **University administration is overflooded by contracts**
- **Increased contract management implicates hiring of an expert.**
- **Until January 2008 contracts were not available in English**
- **Capacity of Access study management database is exhausted. GCLLSG moves database from Access to Oracle.**

CLL4 vs CLL10: Process SAE-Management

	CLL4	CLL10
Sending SAEs to pharma companies	yes	yes
Sending SUSARs to sites, CROs, Ethics Committees and the PEI	no	yes
SAE-Cleaning	yes	yes
SAE-Medical Review	yes	yes
SAE-Evaluation	no	yes
SAE-Reconciliation	no	yes

CLL10
SAE-Management



SAE-Management: current problems

- **Pharma companies pull out of responsibilty for SAE-Management.**
- **SAE-management is labor-intensive. Merely one DCLLSG staff member is on-hand.**
- **Safety Management Database „Vigilance 1„ is not userfriendly and does not allow a scientific evaluation**
- **CLL10-SAEs will be entered in two databases and additionly in an exceltable.**

CLL4 vs. CLL10: onsite-monitoring

	CLL4	**CLL10**
number of onsite-visits	0 (supportive monitoring by phone)	203
monitoring costs: Germany , Austria	0	216.000,00 €
monitoring costs: Czech Republic	0	8.300,00 €
monitoring costs: Switzerland	0	24.000,00 €
total monitoring costs	0	248.300,00 €

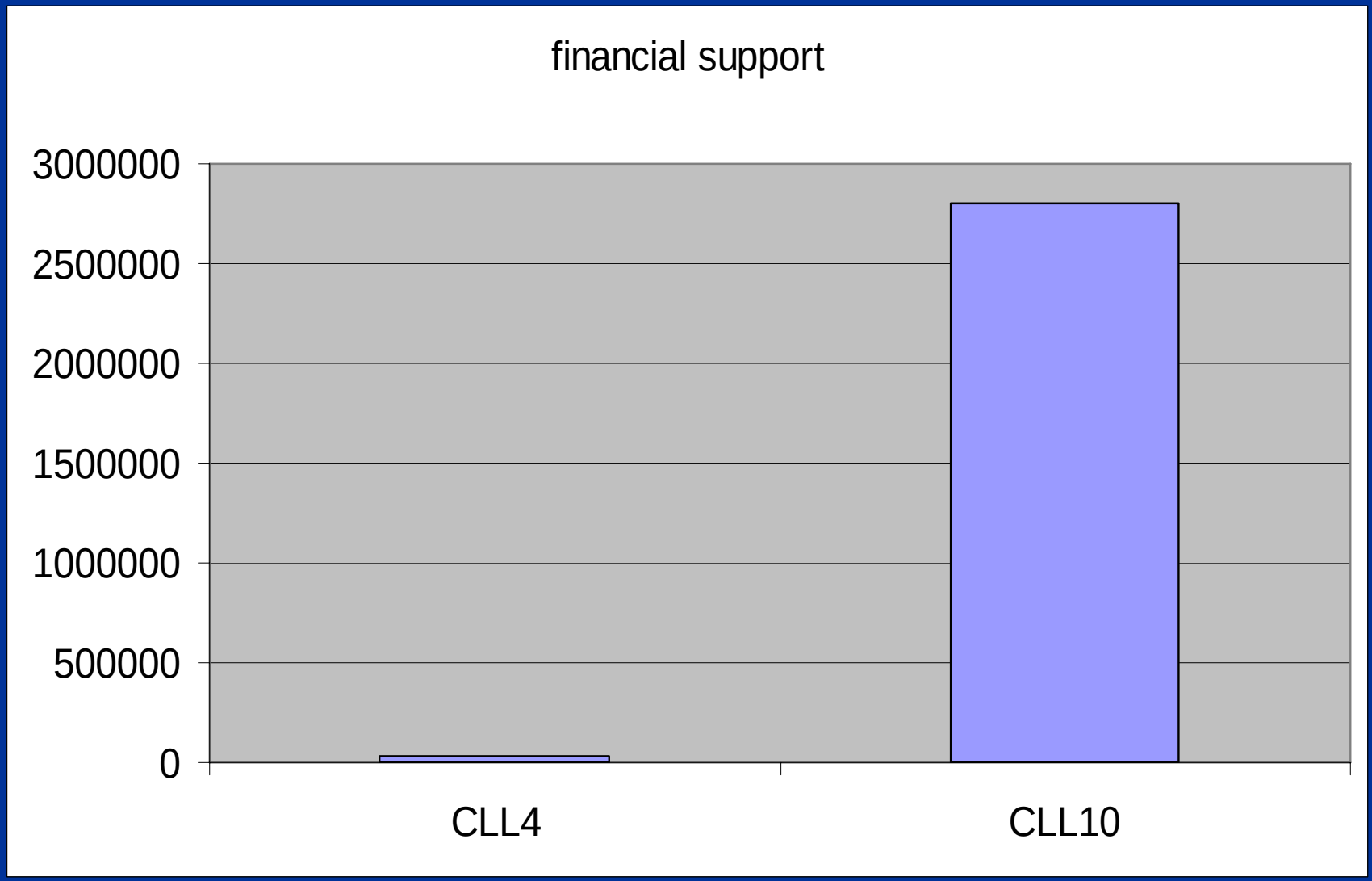
monitoring: current problems

- **Service (Monitoring, preparation of submission..) of global non-academic CROs is not affordable.**
- **Cooperation with academic countryspecific groups increases administrative work and**
- **many documents (monitoring manual, monitoring reporting form) are not available in English.**

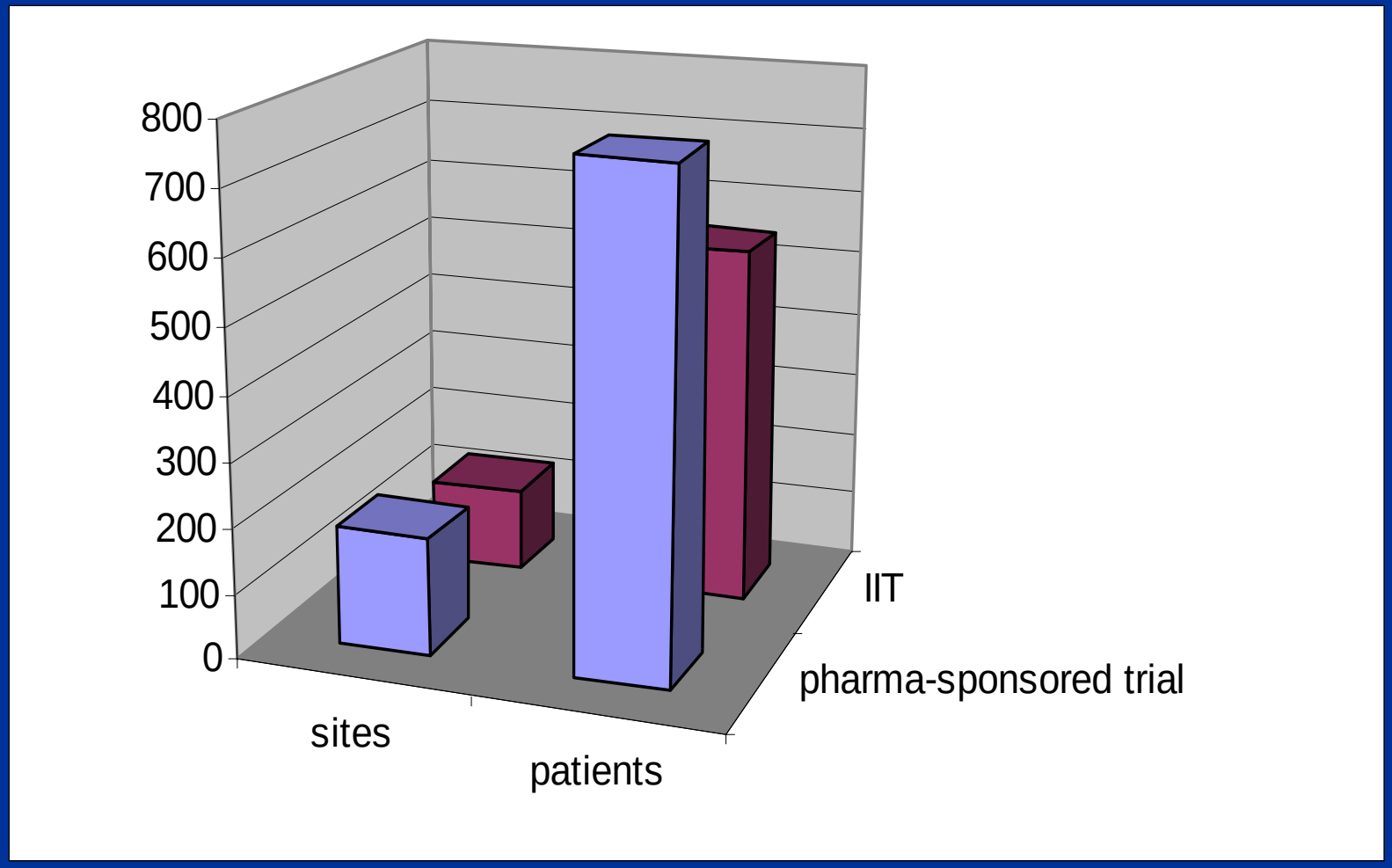
CLL4 vs CLL10: Ethics Submission

	CLL4	CLL10
submission to Coordinating Centre for Clinical Trials (ZKS) to check if GCLLSG is able to fullfill Sponsor's role	no	yes
preparation time for submission	1 week	ZKS: 3 months Ethics: 5 months
number of collected documents from German sites	0	1012
costs: Germany	0 €	27 000€
costs: countries other than Germany	0 €	6 900 € Czech Republic 3 500 € Austria 19 100 € Switzerland

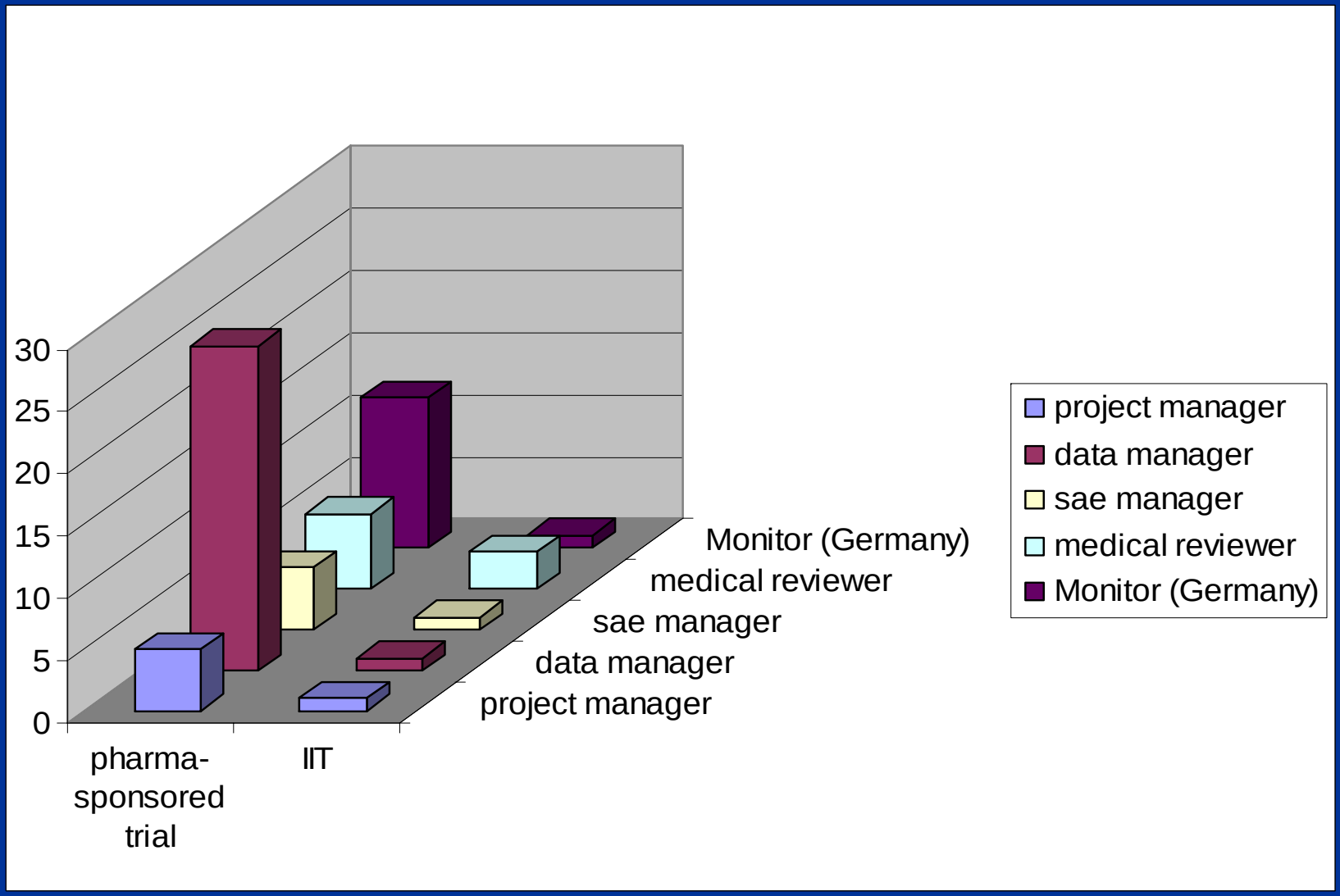
CLL4 vs. CLL10: financial support



IIT vs. Pharma-sponsored trial: size



IIT vs. Pharma-sponored trial: staff



Conclusion

international IITs cannot be performed

according to EU directive 2001

without

an increased financial support and

specialised staff