

The importance of international collaborations in rare diseases the EURAMOS model

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Overview

- Aim of presentation:
 - 1 Introduce rationale for collaborations
 - 2 Clarify central trial structures in EURAMOS model
 - 3 Help understand how we fit together

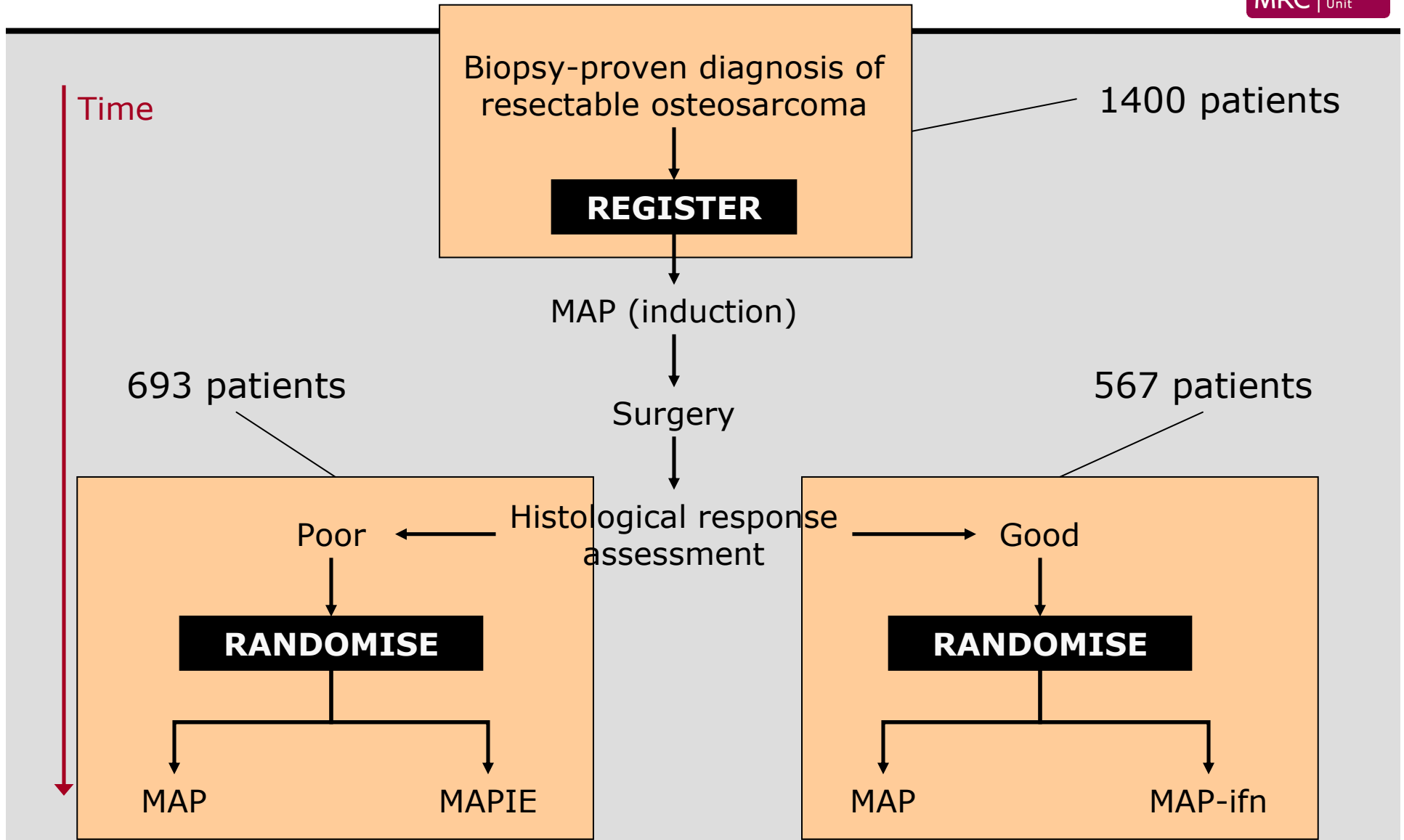
Research & RCTs

- Wish to improve outcomes for all patients
 - Common diseases
 - Rare diseases
- Address right questions at right time
- RCTs provide systematic assessment
 - Randomisation as basis for fair comparison

Osteosarcoma

- Rare disease
 - eg 150 cases/year in UK
- Opportunity to improve outcomes based on risk stratification
 - Two good questions
 1. Good responders
 - Maintenance therapy?
 2. Poor responders
 - Additional drugs?

Design



Typical rare disease

- Reliable answers require many patients
 - Register 1400 patients
 - Randomise 567 Good responders
 - Randomise 693 Poor responders
- Could any single country do this?
 - Clearly not

Typical rare disease

- Reliable answers **and**
- Reasonable time frame because
- Hopefully, further good questions will arise
 - True in osteosarcoma – questions appearing

Intergroups

- Collaborations to work together
 - eg EOI – European Osteosarcoma Intergroup
 - formed 1982
 - mostly northern Europe but some wider trial participation (Chile, Argentina, S Arabia)
 - leads to trials and improved recruitment totals

Intergroups

- 3rd EOI trial (MRC BO06 / EORTC 80931)*
 - second largest OS trial
 - 504 pts over 9yrs from 11 countries
 - **1 patient per week**
- Could EOI-sized group answer our questions?
 - Not quickly, if at all
- Sometimes Intergroups needs to go wider

*Lewis, Nooij, Whelan et al. Improvement in Histologic Response But Not Survival in Osteosarcoma Patients Treated With Intensified Chemotherapy: A Randomized Phase III Trial of the European Osteosarcoma Intergroup. *J.Natl.Cancer Inst.* 99 (2):112-128, 2007.

Large international Intergroups

- EURAMOS Intergroup
 - EOI – western Europe
 - COSS – central Europe
 - SSG – Scandinavia
 - COG – USA + Canada
- Aim for 400 patients/year
 - **7** patients per week
 - 350 patients per year
 - 1400 patients over 4 years

Large international Intergroups

- Sounds easy
 - Maybe, at sites, just like any other research
- Is it easy?
 - No: many challenges
- Can Intergroups work?
 - Yes
 - With care, attention, patience, awareness
 - EURAMOS as an example

What are the challenges?

- Funding
- Sponsorship
- Indemnity
- Knowledge
 - Local processes and national regulations
- Buy-in from sites
- Different practices

Funding



- Key issue – can't run trial without money

Infrastructure

- Requires:
 - 1 Local knowledge & support
 - 2 Central coordination
- Achieve through:
 - 1 Data Centres & National Coordinators
 - 2 Coordinating Data Centre

Infrastructure DCs



Children's Oncology Group
(**COG**)
USA & Canada

Cooperative Osteosarcoma
Study Group (**COSS**)
Austria, Germany,
Hungary, Switzerland

European Osteosarcoma
Intergroup (**EOI**)
Belgium, Netherlands, UK

Scandinavian Sarcoma
Group (**SSG**)
Denmark, Finland,
Iceland, Norway, Sweden

Infrastructure – DC roles

- Appointing National Coordinators
- Identifying legal entity to receive Sponsor's delegated roles
- National applications & submissions
 - Funding
 - Regulatory
 - Ethics
- Patient info sheets & consent forms
- Group-specific protocol appendices
- Collection of data from trial sites

Infrastructure - CDC

- Need central coordination like in single Group trials
 - Lead on common aspects
 - Organise collaboration
 - Improve communication
 - Decrease duplication of tasks

Infrastructure



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Coordinating Data Centre

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CDC roles – before start

- Coordinate Trial Management Group (TMG)
- Lead protocol development
 - Protocol body
 - Common appendices
- Sponsorship
- Registration on trial databases
- Trial website
- Lead agreements between Groups
- Lead negotiations & contracts with Pharma

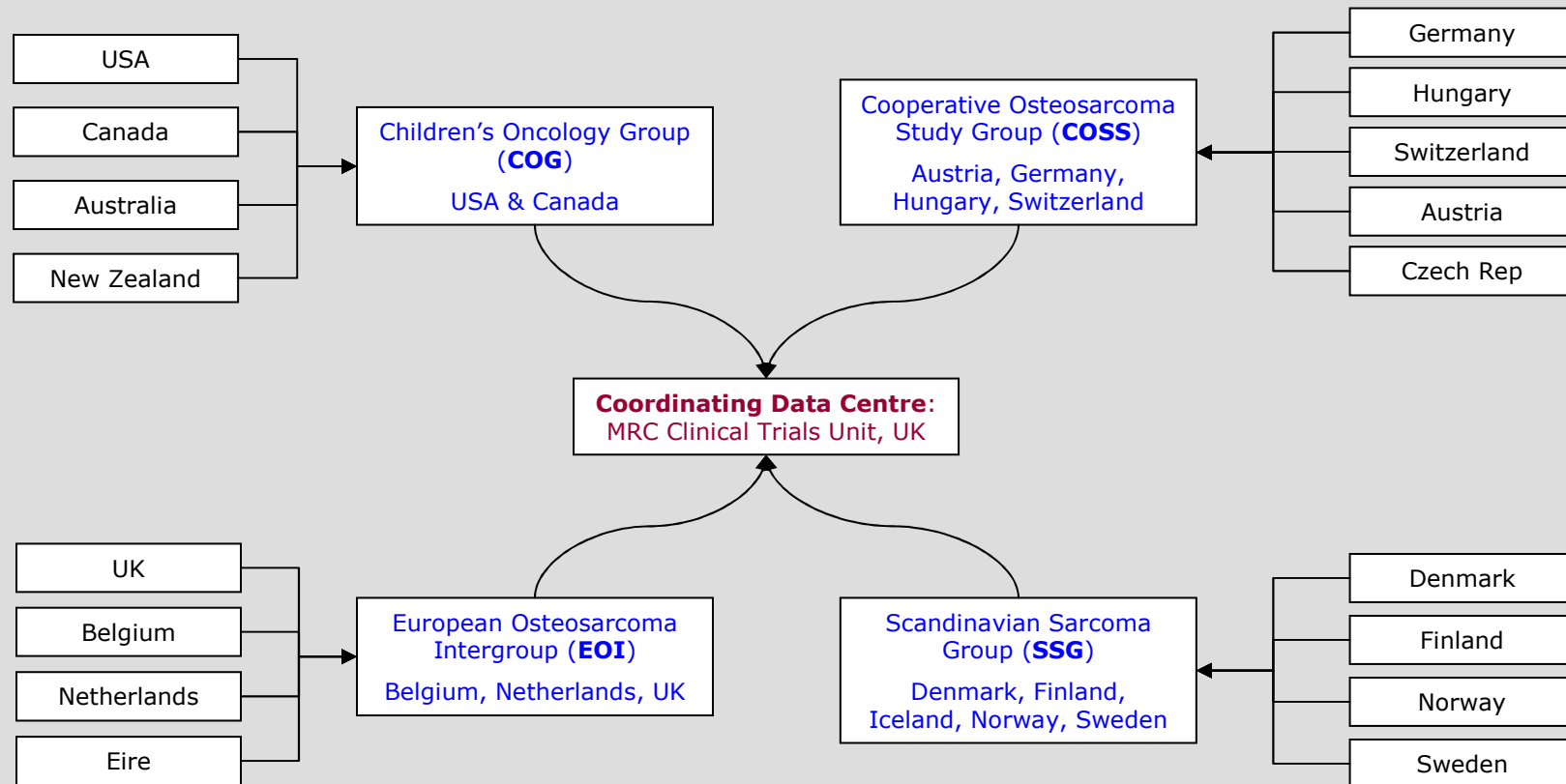
CDC roles – before + during

- Randomisation lists and systems
- Accrual and data reports
- Monitoring of data
- Monitoring of trial sites
- Pharmacovigilance

CDC roles – during + after

- Lead on data collection
 - Define common dataset
 - Produce data flow protocol
 - Centrally compile data from Data Centres
- Coordinate oversight committees
 - Trial Management Group (TMG)
 - Trial Steering Committee (TSC)
 - Independent Data Monitoring Committee (IDMC)
- Lead on analyses

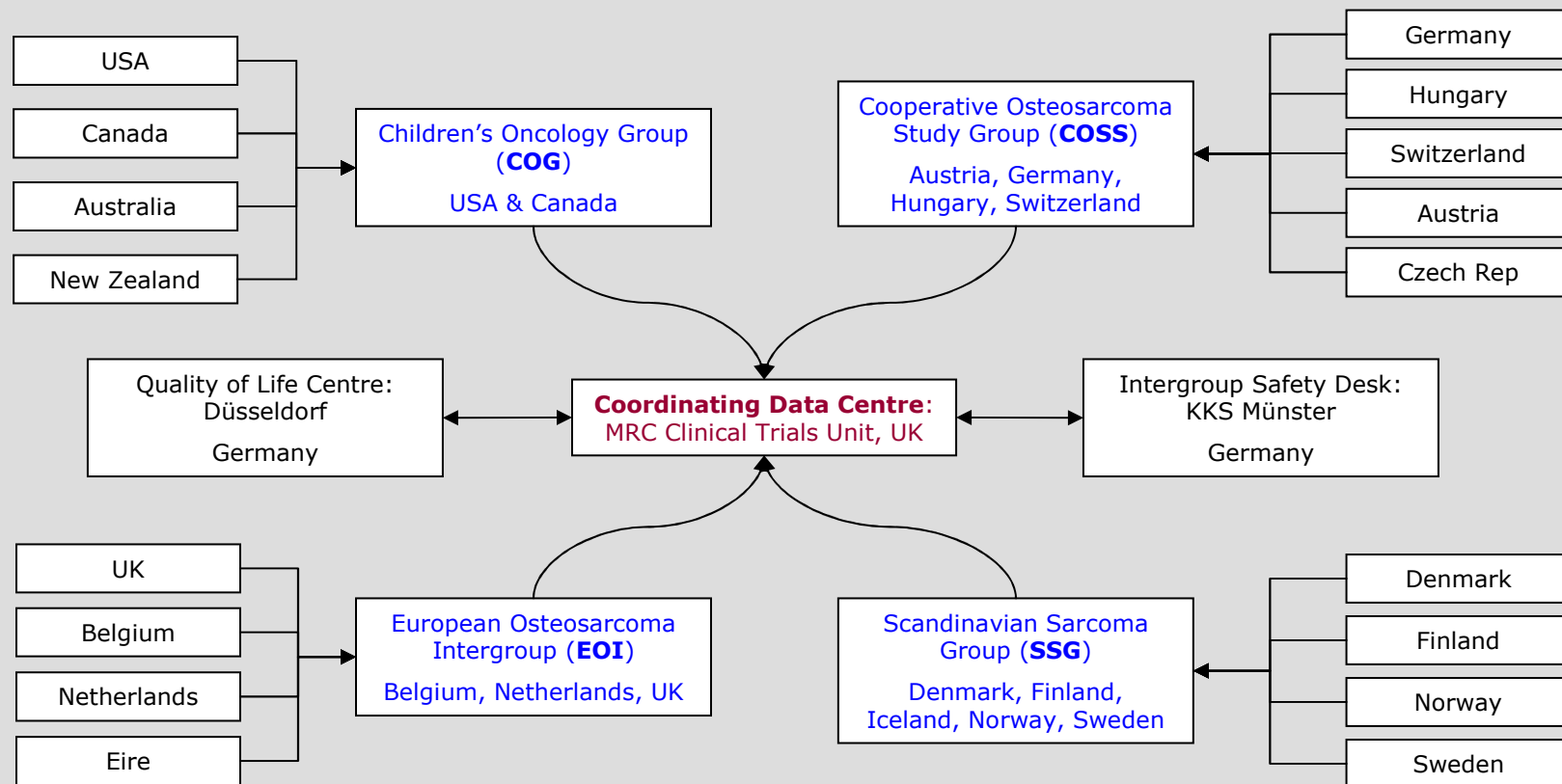
EURAMOS groups + structure



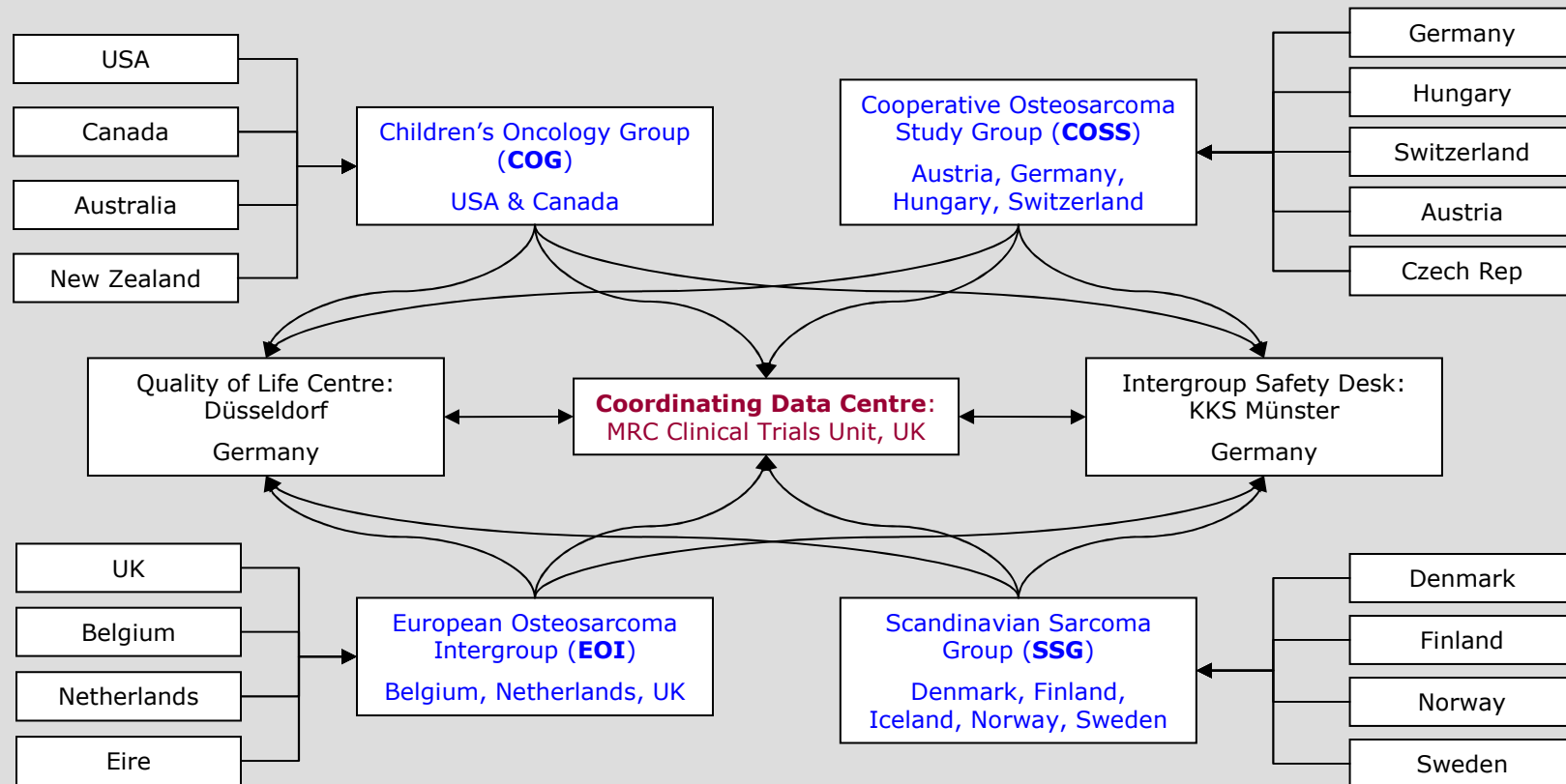
Infrastructure & Delegation

- EU Sponsor can delegate some roles
- CDC can delegate some roles

EURAMOS groups + structure



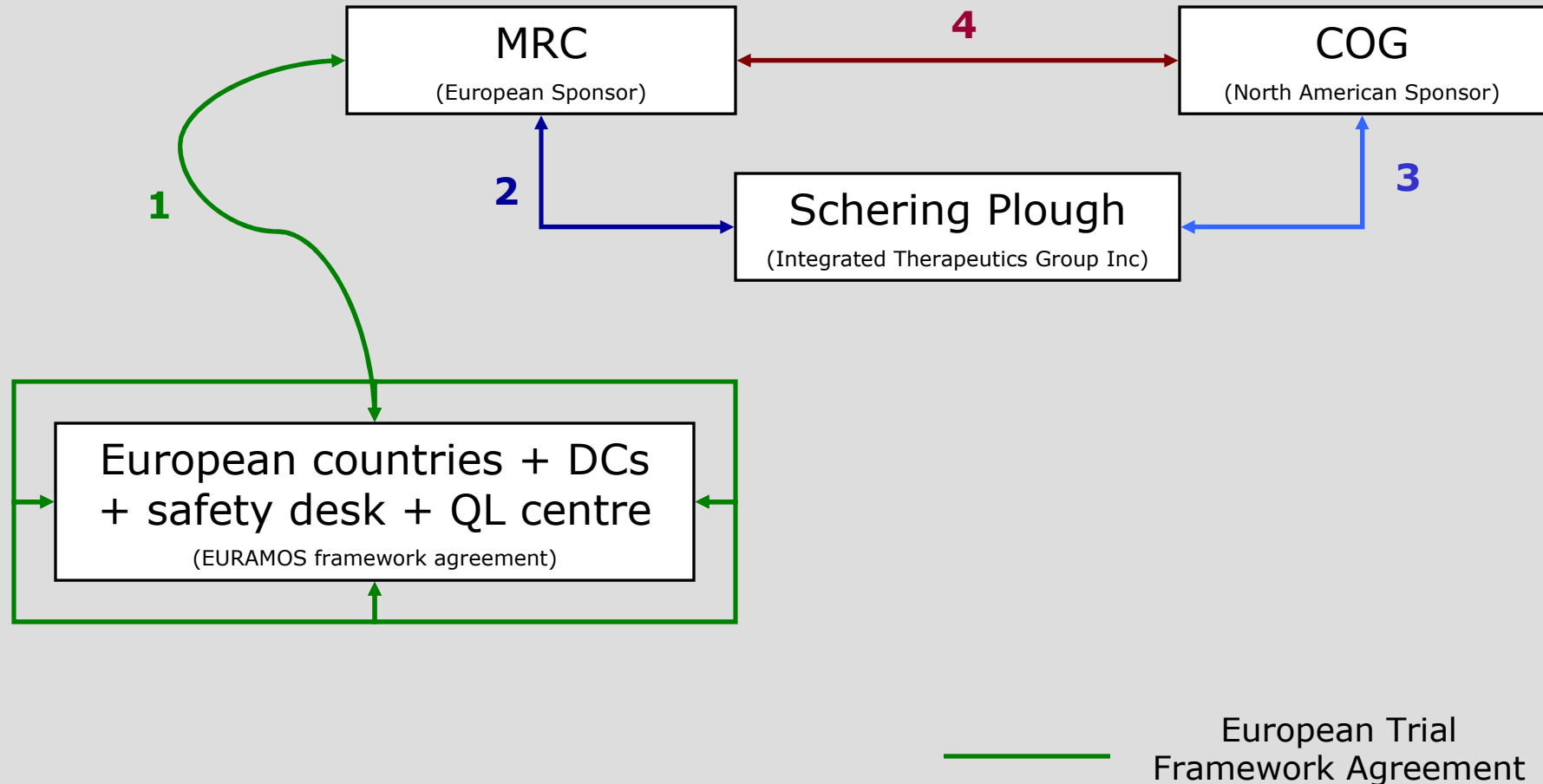
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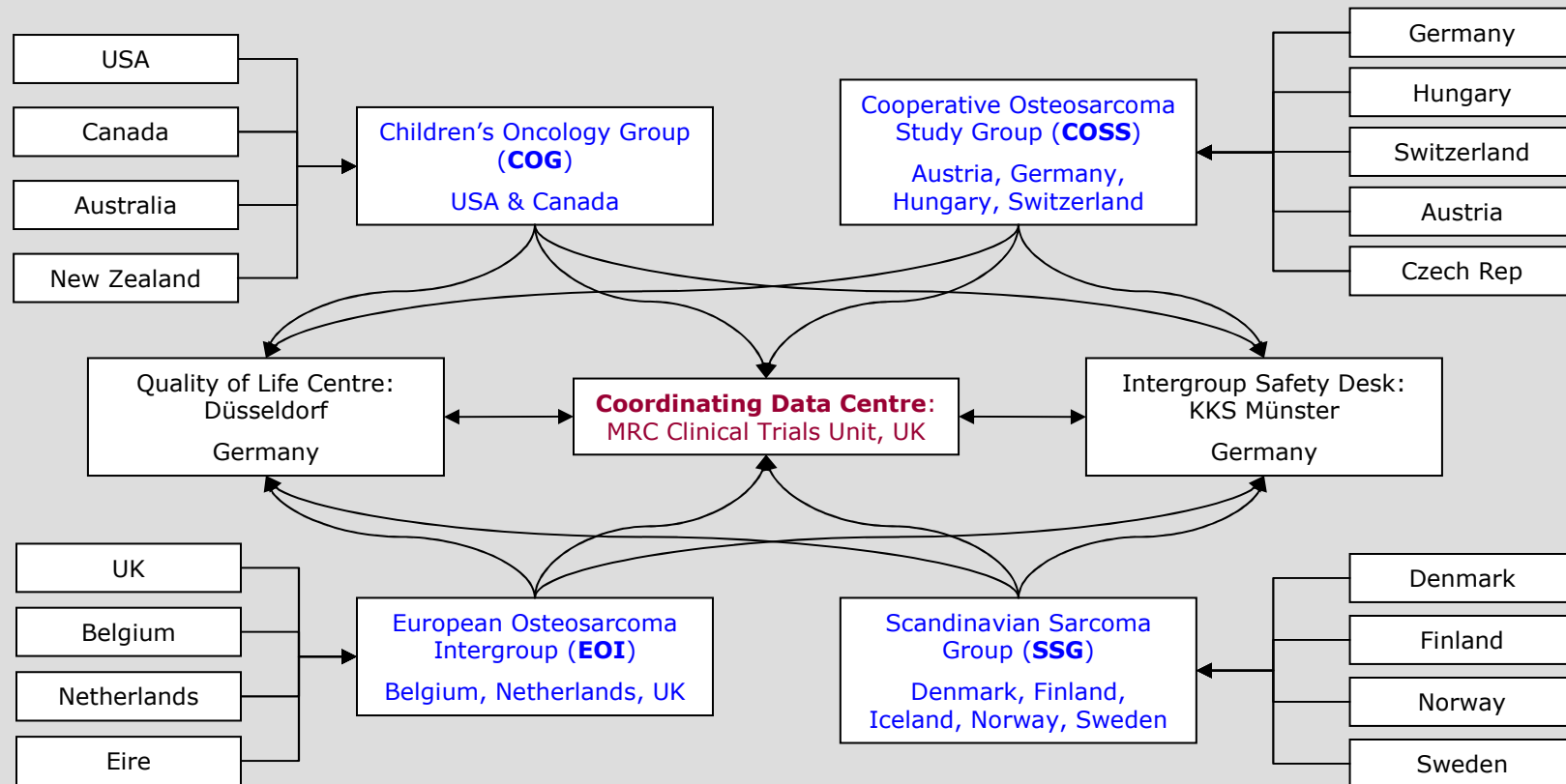
Sponsorship and agreements

- Intergroups as collaborations
 - If no legal existence can't sponsor or sign contract
- Assigning Sponsor
 - MRC (UK) for EU
 - COG (USA) for North America
- Confirmation of Sponsor
 - Development of agreements
- Planned for Sponsor in each country
 - Legal entity in place as local delegate

Major agreements & contracts



EURAMOS groups + structure

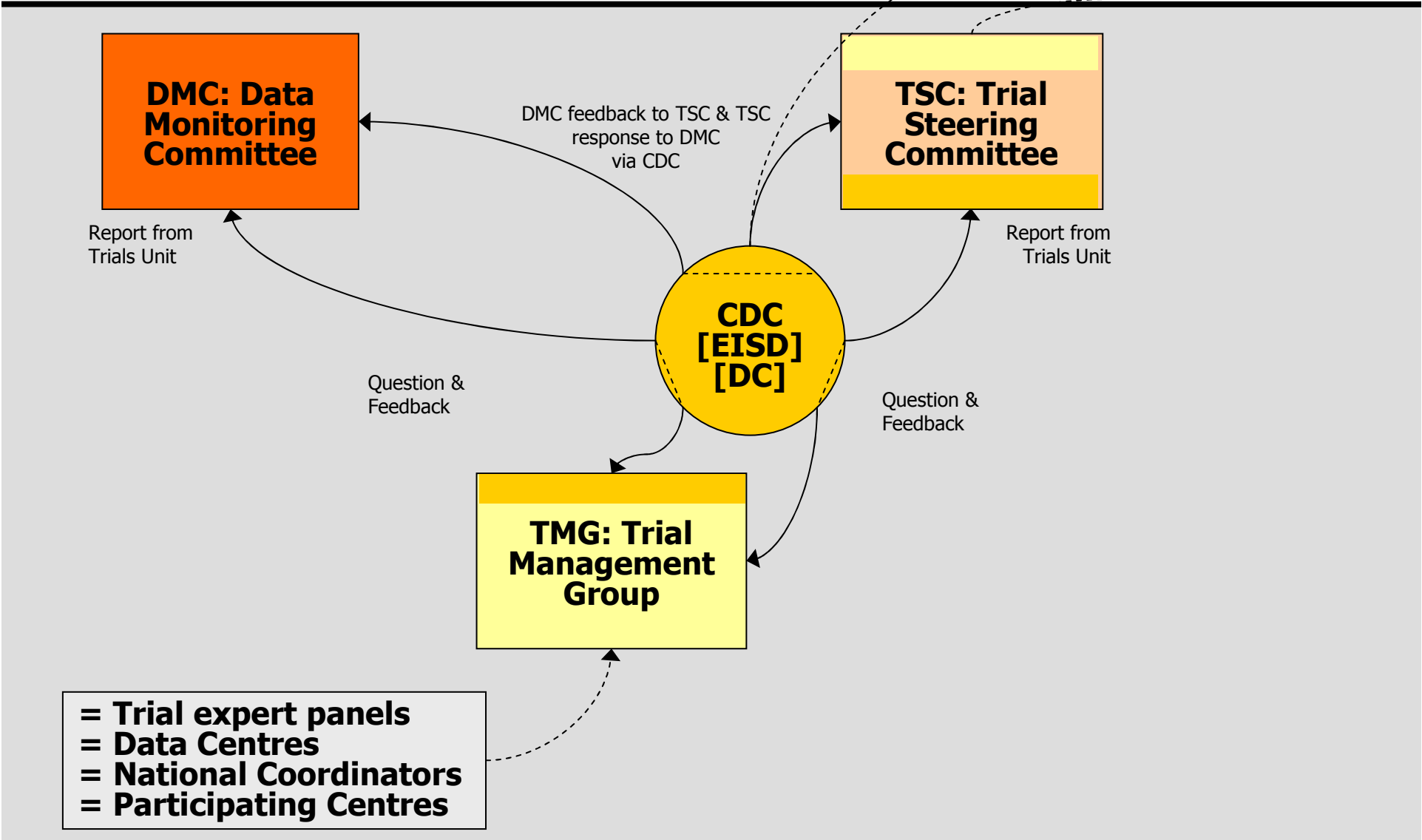


Funding

- How to ensure fair and representative funding for central and local infrastructure?
- EURAMOS funded through ESF
 - Part of ECT-EUROCORES
- Distributed funding
 - National funders
- Central support
 - ESF

Oversight bodies

- Trial Management Group
 - **TMG**
 - Day-to-day running
- Trial Steering Committee
 - **TSC**
 - Oversight
- Independent Data Monitoring Committee
 - **IDMC**
 - Review of accruing data



International collaborations

- RCTs are feasible in rare diseases
- Requires collaboration
- Collaboration is achievable
- EURAMOS is one model