

EURAMOS-1 infrastructure

Practical issues: common data and CDC role

Matthew Sydes

Trial Statistician

MRC Clinical Trials Unit, London, UK

Overview

- EURAMOS-1 trial has an individual structure
- This session to:
 - Introduce or reiterate trial structures
 - Contribute to understanding of trial, overall

Overview

- Coordinating Data Centres & Data Centres
- Trial Committees
 - Trial Management Group
 - Trial panels
 - Data Monitoring Committee
 - Trial Steering Committee
- Data transfer processes

Why international trials?

- Rare disease
 - eg osteosarcoma = 150 cases/years in UK
- Need international trials to
 - answer pivotal questions reliably in reasonable timescale
 - from national or collaborative groups
- EURAMOS Intergroup
 - EOI – western Europe
 - COSS – central Europe
 - SSG – Scandinavia
 - COG – USA + Canada
- Aim for 400 patients/year
 - **7** pts/wk

Why have a CDC?

- Need central coordination like in single Group trials
 - Lead on common aspects
 - Organise collaboration
 - Improve communication
 - Decrease duplication of tasks
- Data Centre (DC) from each Group
 - CDC in addition to DCs
 - DCs have local expertise
 - Different countries with different regulations
 - National Coordinators

EURAMOS groups + structure

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

EURAMOS groups + structure

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

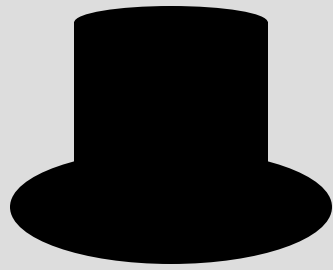
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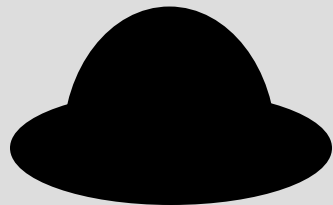
MRC CTU's 3 hats



EURAMOS Coordinating Data Centre

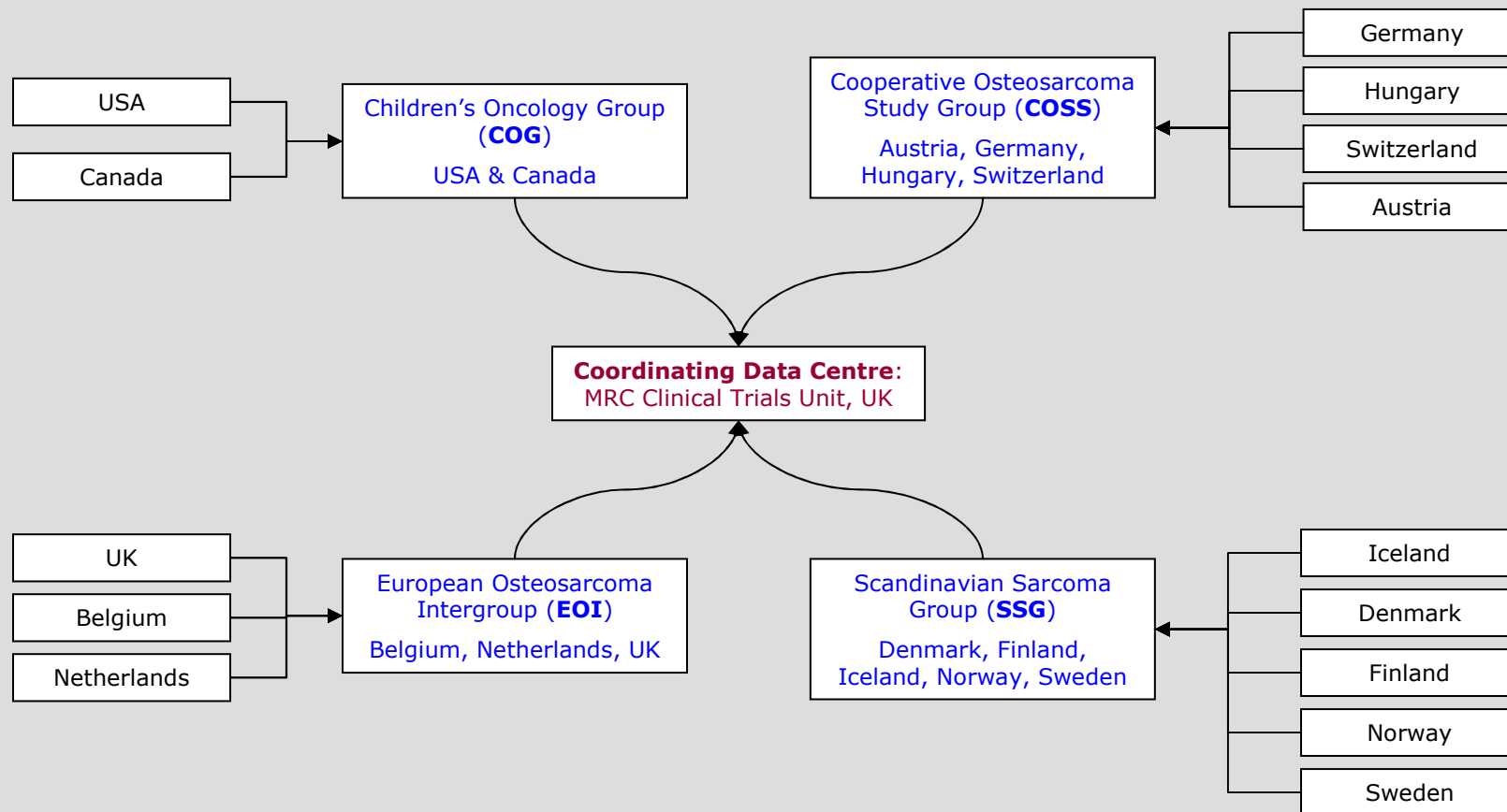


EOI Data Centre



UK representative

EURAMOS groups + structure



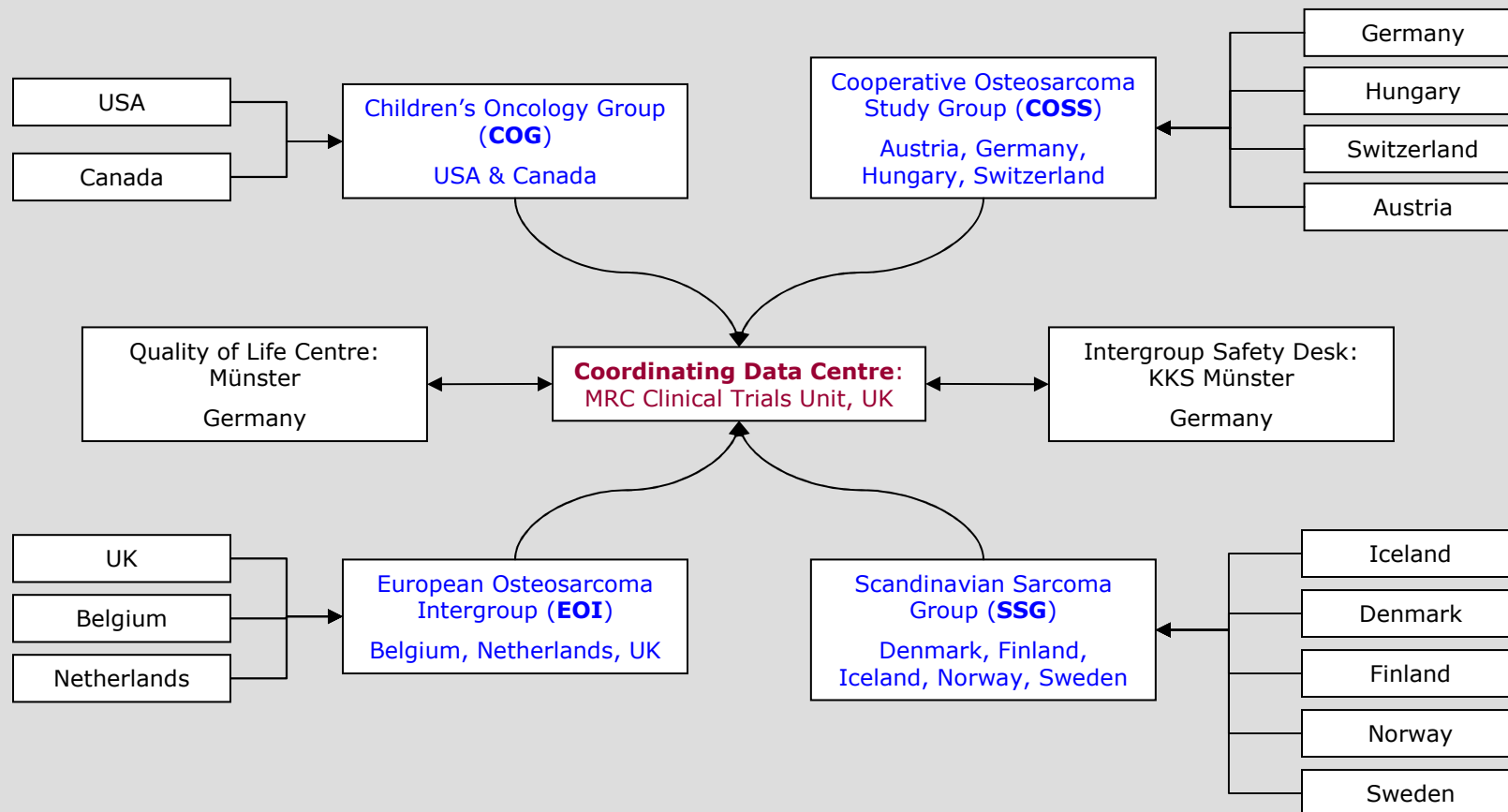
CDC roles – before start

- 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 and contracts with drug companies

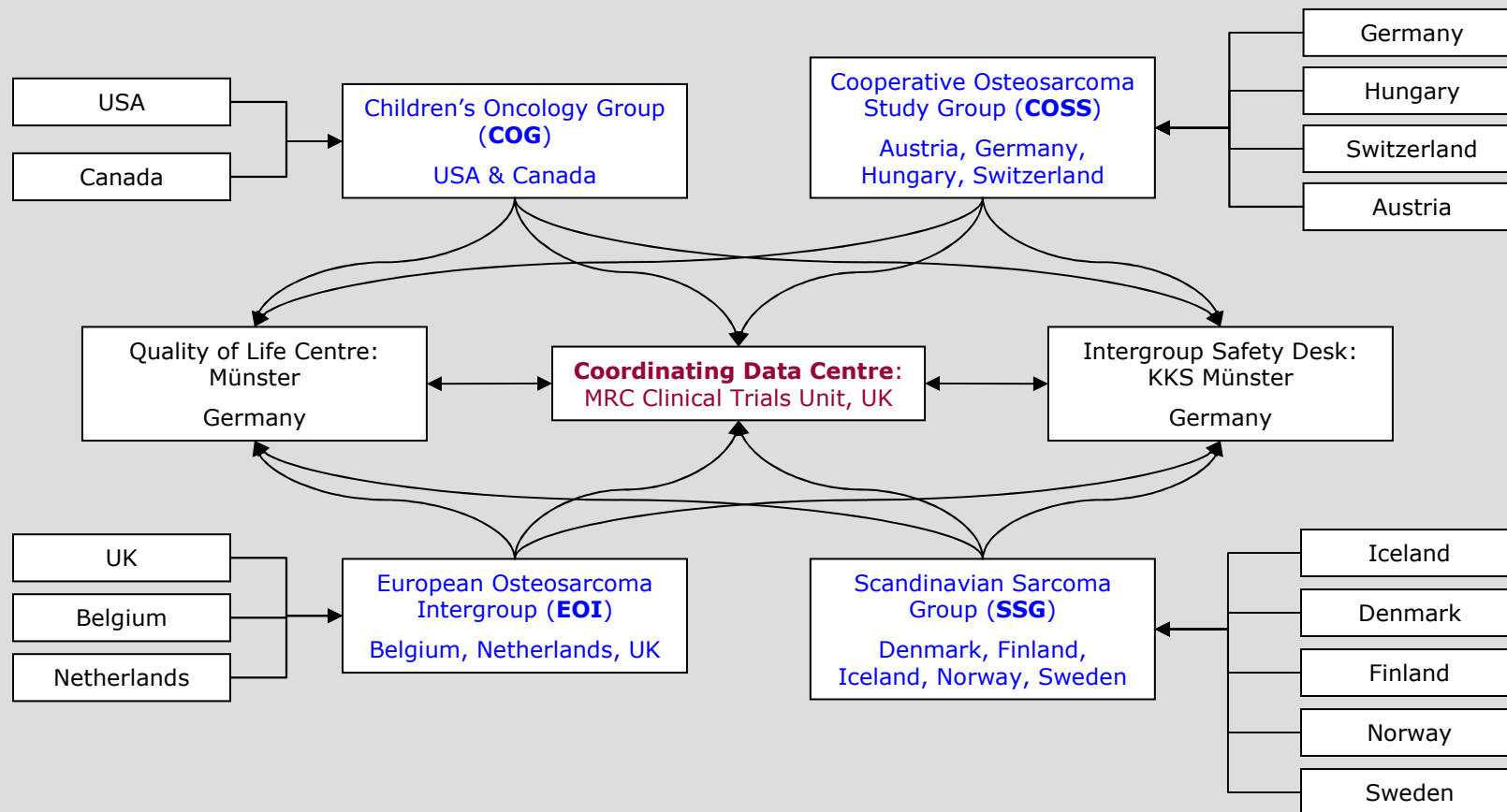
CDC roles – before + during

- Lines of communication
 - Randomisation lists and systems
 - Accrual and data reports
 - Some monitoring of data
 - Monitoring of trial sites
 - Pharmacovigilance
-
- Sponsor can delegate some roles
 - CDC can delegate some roles

EURAMOS groups + structure



EURAMOS groups + structure



CDC roles – during + after

- Lead on data collection
 - Define common dataset
 - Produce data flow protocol
 - Centrally compile data from Data Centres
- Coordinate Trial Steering Committee (TSC)
- Coordinate Independent Data Monitoring Committee (IDMC)
- Lead on statistical analysis plan
- Perform analyses (final and interim)
- Coordinate publication

CDC role

- Coordinating role
- Panels
 - Oncology
 - Surgery
 - Radiology
 - Pathology
 - QL
 - Statistics
 - Biology
- Buy in and ownership – broad involvement

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Roles of DCs

- Regional knowledge and buy-in
- Appointing National Coordinators
- Identifying legal entity to receive Sponsor's delegated roles
- National funding applications
- National regulatory applications
- National and local ethics submissions
- Patient info sheets & consent forms
- Group-specific protocol appendices
- Collection of data from trial sites

National Coordinators

- Provide local / national expertise
- Ensure that trial is conducted according to
 - GCP
 - Local laws and regulations

Oversight bodies

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

TMG

- Trial Management Group (**TMG**) is main body for trial organisation
- Broad, international representation
- Manage the day-to-day running of the trial
- Input from various groups

TMG: Trial Management Group

Participating Centres

National Coordinators

Pharmacy panel

Quality of life panel

Statistics panel

Radiotherapy panel

Radiology panel

Surgical panel

Biological Studies panel

Pathology review panel

Oncology panel

COG Data Centre

COSS Data Centre

EOI Data Centre

SSG Data Centre

CDC

EISD

QLCC

Oncology panel

- Remit
 - Check protocol for content, consistency and accuracy on all topics surrounding study medication.
 - Consultation on chemotherapy during trial
- Membership
 - 28

Pathology review panel

- Remit
 - Ensure histopathological criteria for eligibility
 - Timely and consistent assessments
 - Review diagnostic biopsy & resection specimen
 - Regular audit
- Membership
 - 23

Biology studies panel

- Remit
 - Development of biology study protocols
 - Use uniform methodology between groups
- Membership
 - 28

Surgical panel

- Remit
 - Offer guidance on tumour resection
 - Offer guidance on reconstruction
- Membership
 - 17

Radiology panel

- Remit
 - Issue guidance on imaging of primary tumour
 - Issue guidance on imaging of metastases
 - Assist in determining metastatic status
 - Review thorax CT scans
- Membership
 - 13

Radiotherapy panel

- Remit
 - Issue guidance on RT
- Membership
 - 4

Statistics panel

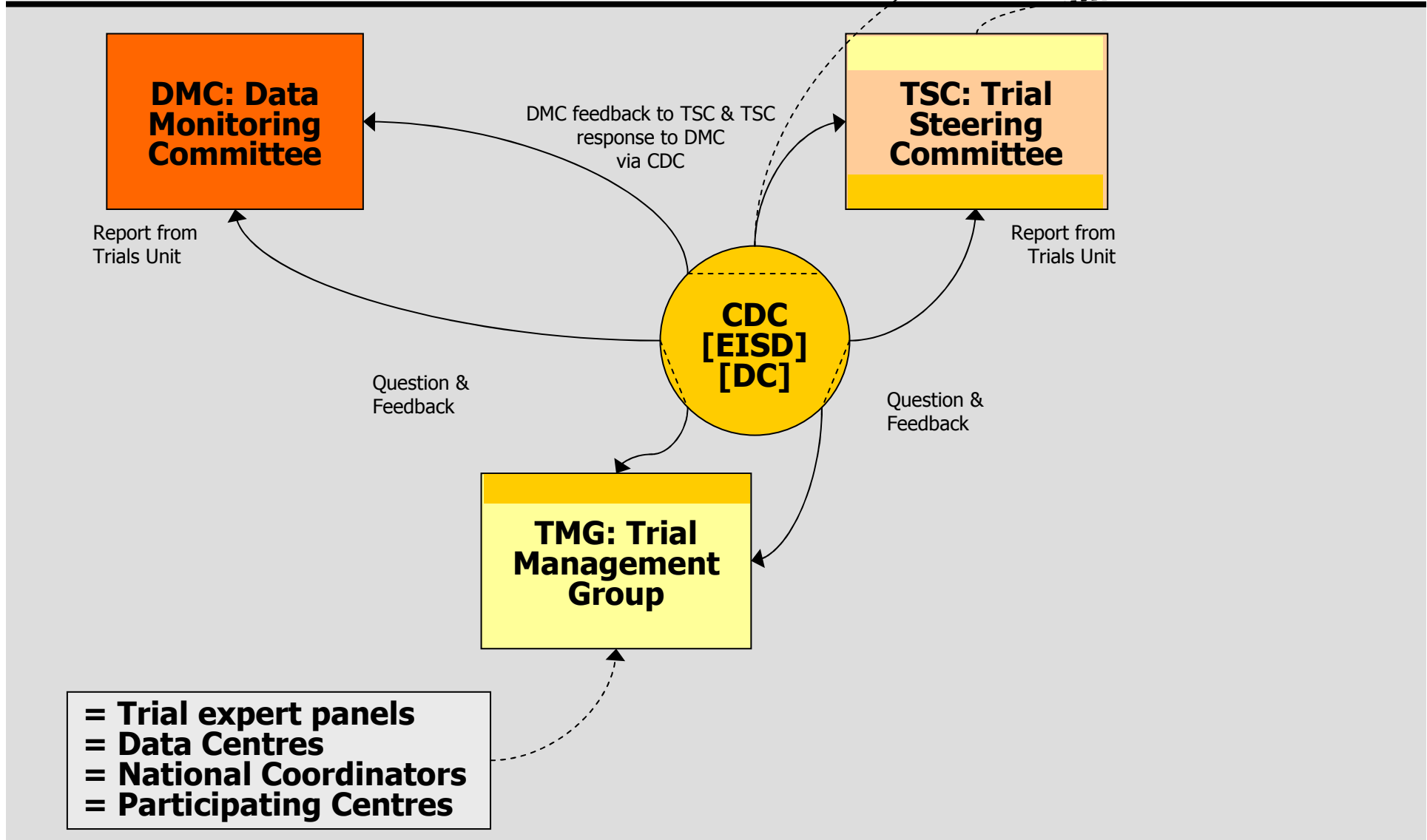
- Remit
 - Input into all aspects of design, data storage, data management and evaluation
 - Develop a statistical analysis plan
- Membership
 - 4

Quality of life panel

- Remit
 - Issue guidance on QL
 - Select QL instruments
 - Guide administration of questionnaire
- Membership
 - 6

Pharmacy panel

- Remit
 - Issue guidance on trial medication
- Membership
 - 4



IDMC

- Remit
 - To safeguard the interests of trial's participants, potential participants, investigators and sponsor
 - To assess the safety and efficacy of the trial's interventions, and to monitor the trial's overall conduct and ethics thereby protecting its validity and credibility
- Membership
 - 5
 - All independent members
 - Nominated by each group

IDMC

- Huge variety in the way IDMCs have been structured
- Format & structure based on DAMOCLES
 - The DAMOCLES study group. A proposed charter for clinical trial Data Monitoring Committees: helping them to do their job well. Lancet 2005, 365: 711-722
- Formal charter

IDMC charters

- Lack of guidance or standard operating procedures for DMCs
 - Charter produces clarity from variety
- Systematic and transparent approach
 - Structure
 - Operation
 - Policy
 - Process

Roles & responsibilities

Specific roles of the committee

To provide interim review of the trial's progress by:

- assessing data quality, including completeness (thereby encouraging collection of high quality data)
- monitoring recruitment figures and losses to follow-up
- monitoring compliance with the protocol by participants and investigators
- monitoring evidence for treatment differences in the main efficacy and safety outcome measures – and thus recommending action when/whether the main trial question has been answered

Roles & responsibilities

//cont

Specific roles of the committee

monitoring evidence for treatment harm e.g. toxicity, SAE's, deaths
 recommending whether the trial should continue to recruit or follow-up
 recommending any major changes to the protocol, where necessary (e.g. changes to the recruitment procedures, inclusion criteria, endpoints, data collection, etc)
 advising on and/or endorsing any major protocol modifications suggested by investigators or sponsors (e.g. changes to the inclusion criteria, endpoints, data collection, etc)

Roles & responsibilities

//cont

Specific roles of the committee

monitoring planned sample size with regards (i) *a priori* assumptions about the control arm outcome and (ii) emerging differences in clinical relevant subgroups

suggest additional data analyses

assessing the impact and relevance of any external evidence provided

monitoring compliance with previous IDMC recommendations

considering the ethics of the trial

The IDMC should **not** have a role in increasing or decreasing the planned sample size as it is not blind to the current results of the trial.

Relationships

Clarification of whether the IDMC are advisory (make recommendations) or executive (make decisions)

The IDMC are advisory to the TSC.

The TSC is the executive body for the trial. It contains representatives of the investigators and independent members.

Organisation of meetings

Whether meetings will be face-to-face or by teleconference

The first meeting should be face-to-face. It is recommended that the IDMC meet face-to-face at least once a year for subsequent meetings, with teleconference as a second option. At least one of the CIs should try to attend in person if the IDMC request their presence.

Trial documentation

Will the IDMC be blinded to the treatment allocation?

The IDMC will not be blinded to the identity of the treatment arms.

Trial documentation

Who will see the accumulating data and interim analysis?

Interim data and analyses by treatment group (and the deliberations of the IDMC) should be available only to those present in the closed sessions i.e. only members of the IDMC and CDC staff who attend the closed session. Permission must be sought from the IDMC to circulate the report to non-clinical staff at the other participating data centres.

IDMC members must not share confidential information with anyone outside the IDMC, including the CIs.

Decision making

What decisions / recommendations will be open to the IDMC

The possible recommendations are numerous and could include:-

- No action needed, trial continues as planned
- Early stopping due to, amongst other things, clear benefit or harm of a treatment, safety concerns on secondary outcome, slow recruitment, or external evidence
- Stopping recruitment within a subgroup
- Extension of recruitment/follow-up
- Advising on or proposing protocol changes

Decision making

How decisions or recommendations will be reached within the IDMC

The role of the chair should be to summarize discussions and encourage consensus. In each area of discussion the chair should give their own opinion last.

Every effort should be made for the IDMC to reach a consensus. If the IDMC cannot achieve consensus, a vote should be taken...

IDMC

- Meetings and review of data
 - May 2006
 - Oct 2006
 - May 2007
 - Nov 2007
- Recommended continuation of trial
- Next meeting
 - Dec 2008 in London, UK

Trial Steering Committee

- Remit
 - Provide overall supervision
 - Provide advice on all aspects of the trial
- Membership
 - n=10 including:
 - 1 independent TSC Chair
 - 3 other independent members
 - 4 non-independent Group Chief Investigators
 - 1 non-independent TMG Chair
 - 1 non-independent CDC representative

Trial Steering Committee

- Formal charter
 - Formalise roles, responsibilities
 - Based on DMC Charter template
 - Set out preferences for meetings & formats

- TSC to receive standard report from CDC
- TSC to receive feedback from IDMC
- TSC to meet after IDMC meetings

Trial Steering Committee

- Monitoring and supervising progress of trial towards its interim and overall objectives
- Consider recommendations of the IDMC (which should include comments on any relevant evidence external to the trial)
- Monitoring trial progress and maximizing chances of completing the study within time scale set by funders
- Approving any changes to the trial protocol

[selected]

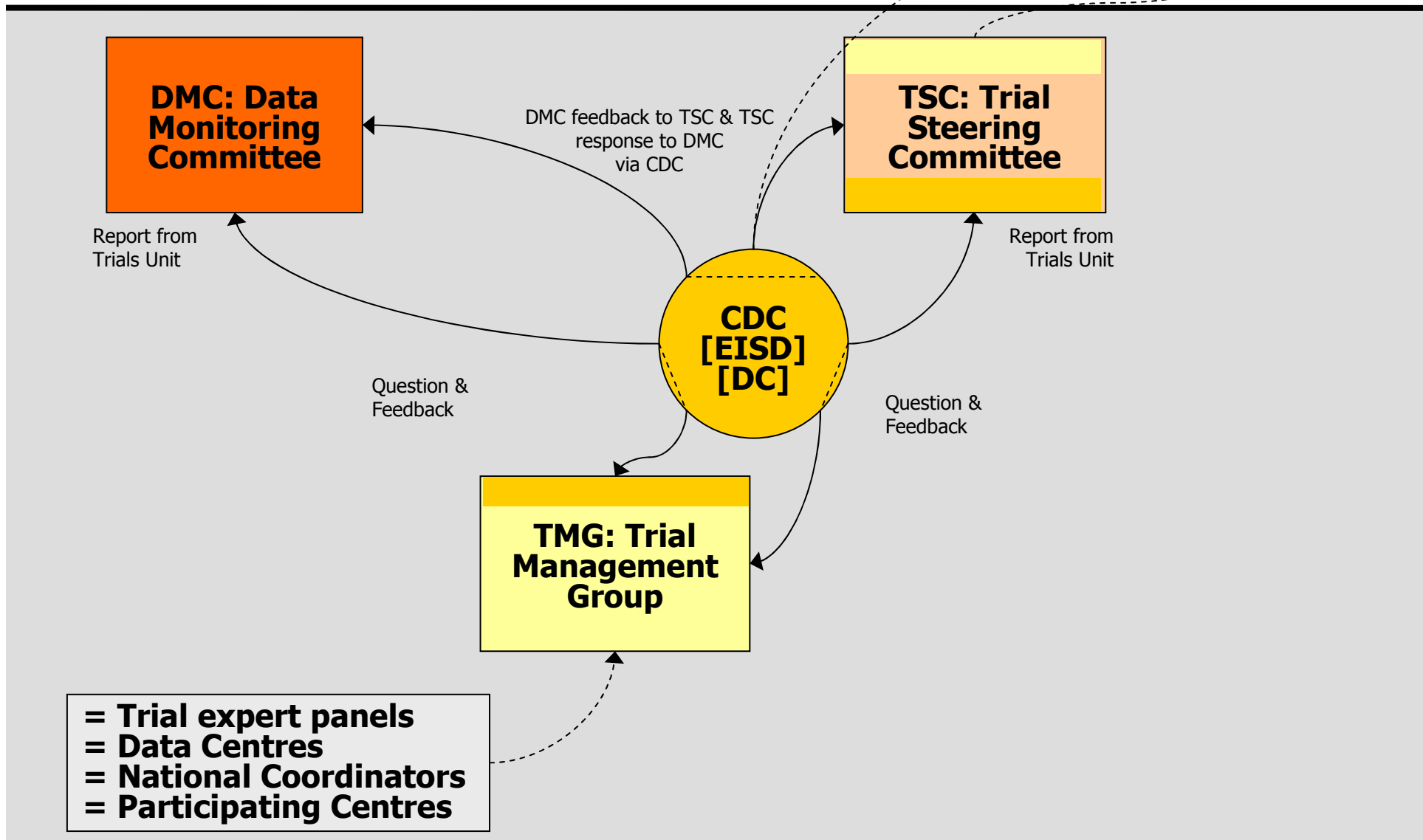
Trial Steering Committee

Possible decisions could include:-

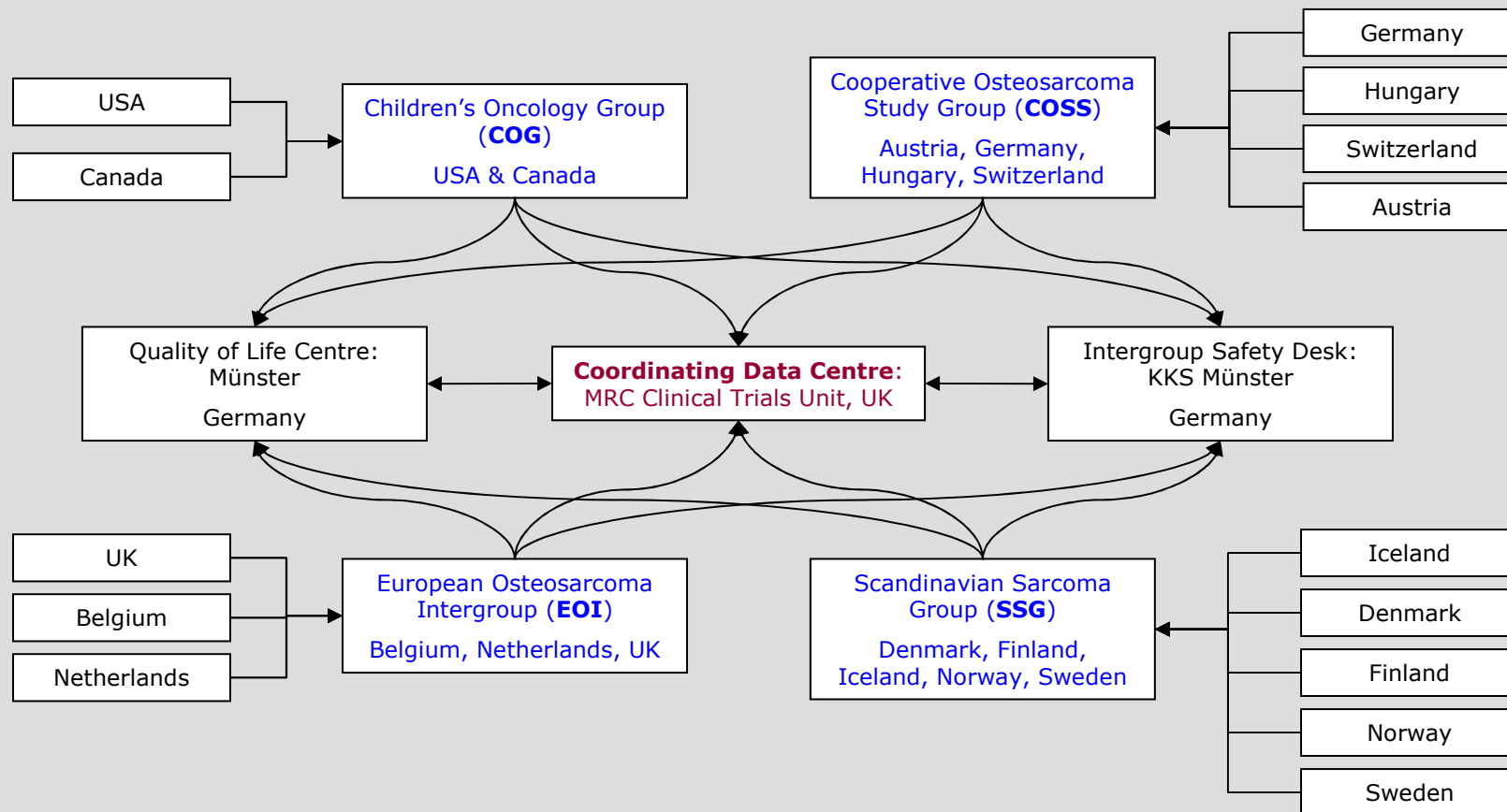
- No action needed, trial continues as planned
- Early stopping due to, amongst other things, clear benefit or harm of a treatment, safety concerns on secondary outcome, slow recruitment, or external evidence
- Stopping recruitment within a subgroup
- Extension of recruitment/follow-up
- Protocol changes
- Changes to target sample size
- Action for certain centers

Trial Steering Committee

- Every effort should be made for the TSC to reach a consensus
- If the TSC cannot achieve consensus, a vote should be taken by the independent members only (i.e. PIs should not have voting rights in the TSC)



EURAMOS groups + structure



Data structures

- Data requirements differ by group
 - Different coding and presentational styles
 - Collection methods: Paper vs on-line
 - Data for associated projects

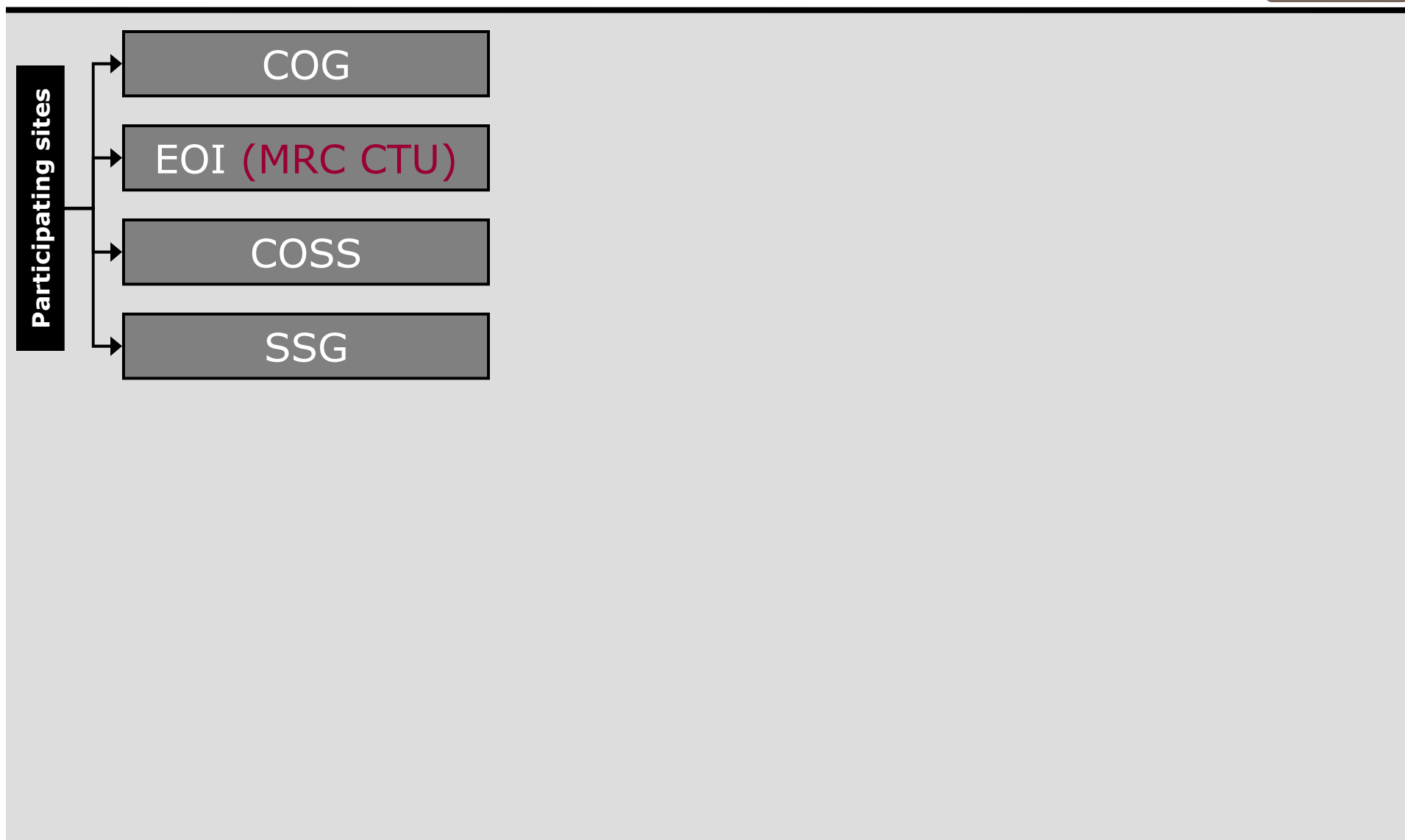
Data structures

- Take approach that is simplest for sites
 - Use group-standard methods
 - Let trial infrastructure cope from there
- Common Data Set
 - All group's CRFs map to the CDS
 - CDS as basis for all analyses
- Data Transfer Protocol
 - Data sent to CDC at least twice a year

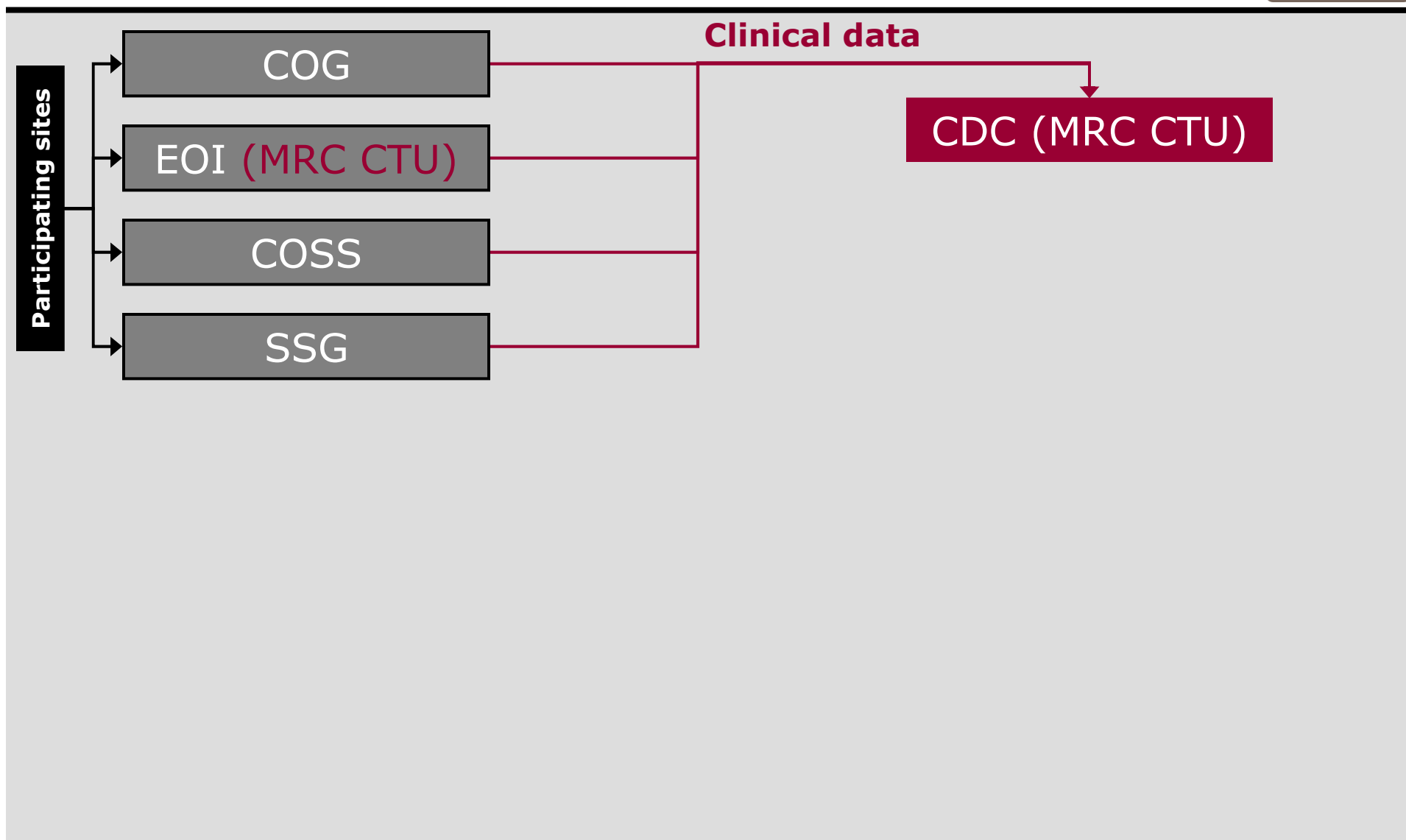
EURAMOS dataflow

Participating sites

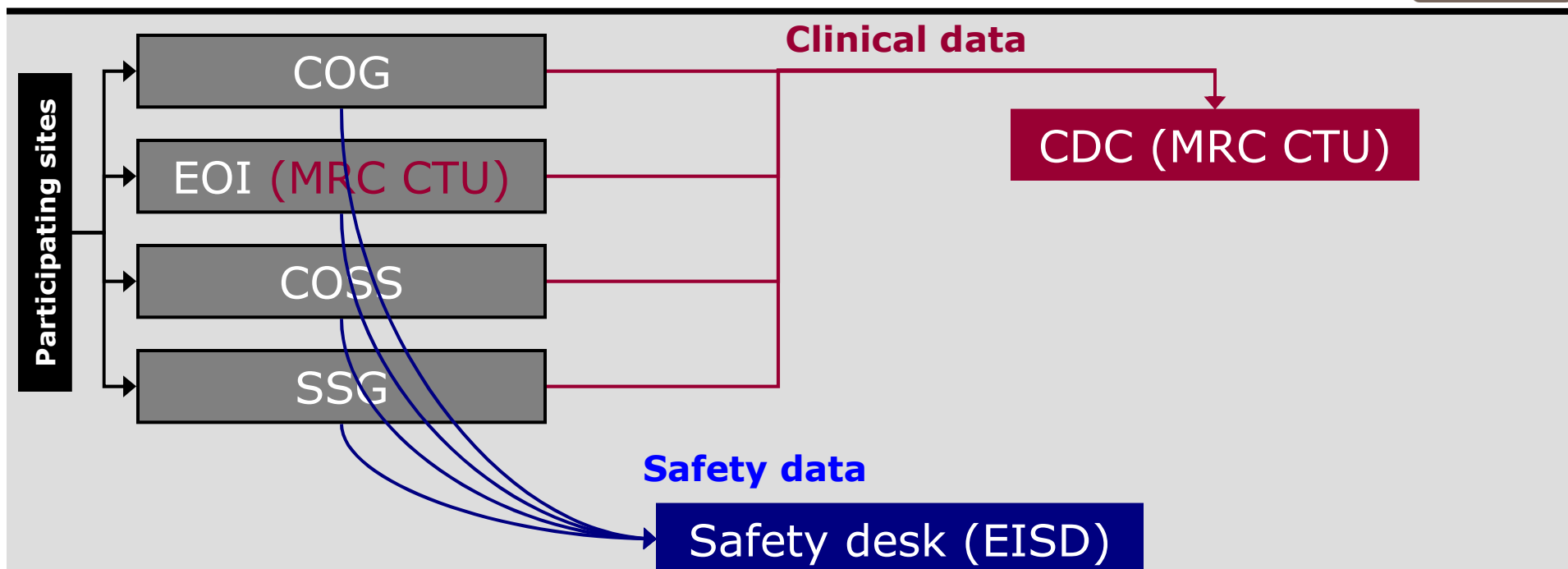
EURAMOS dataflow



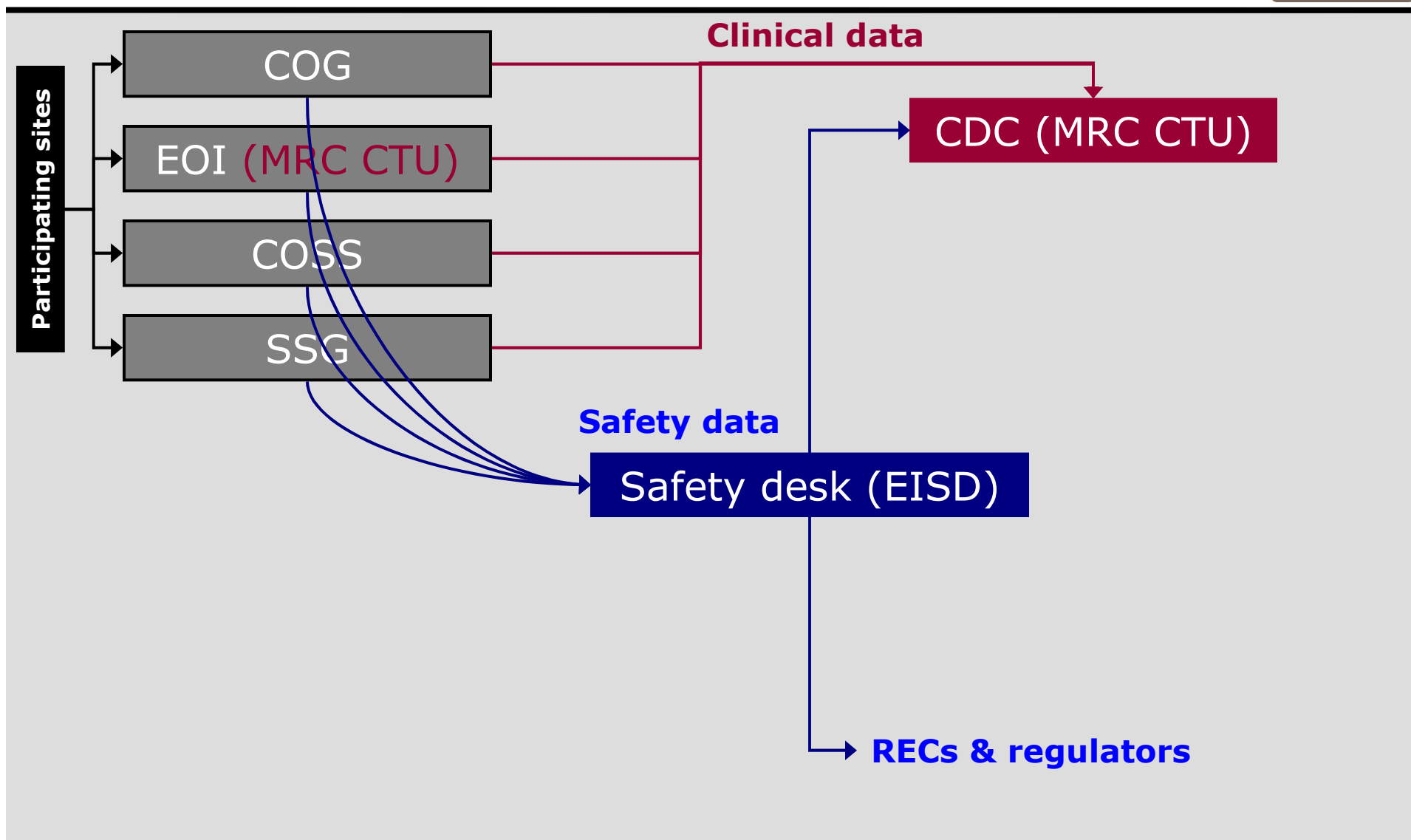
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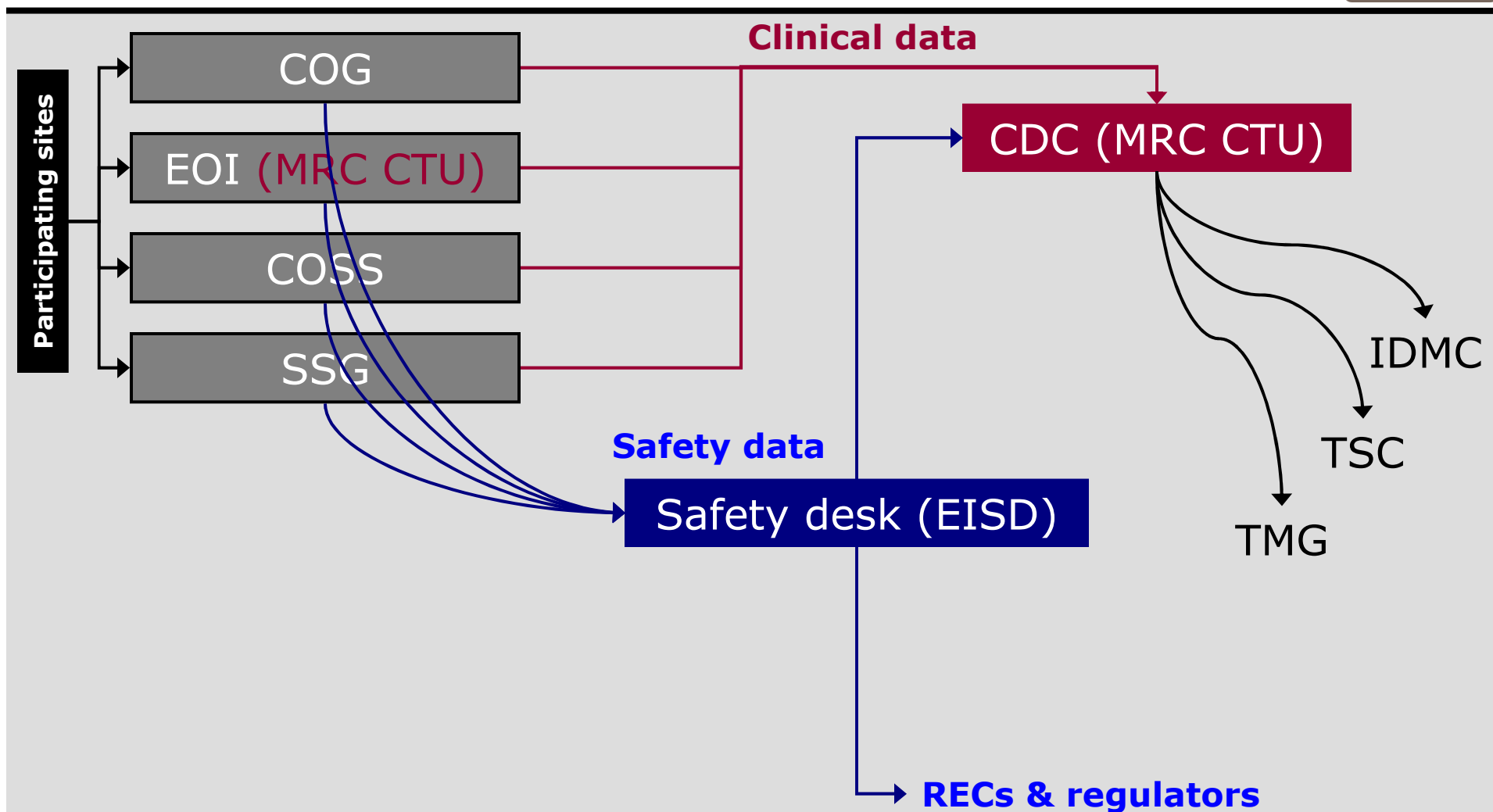
EURAMOS dataflow



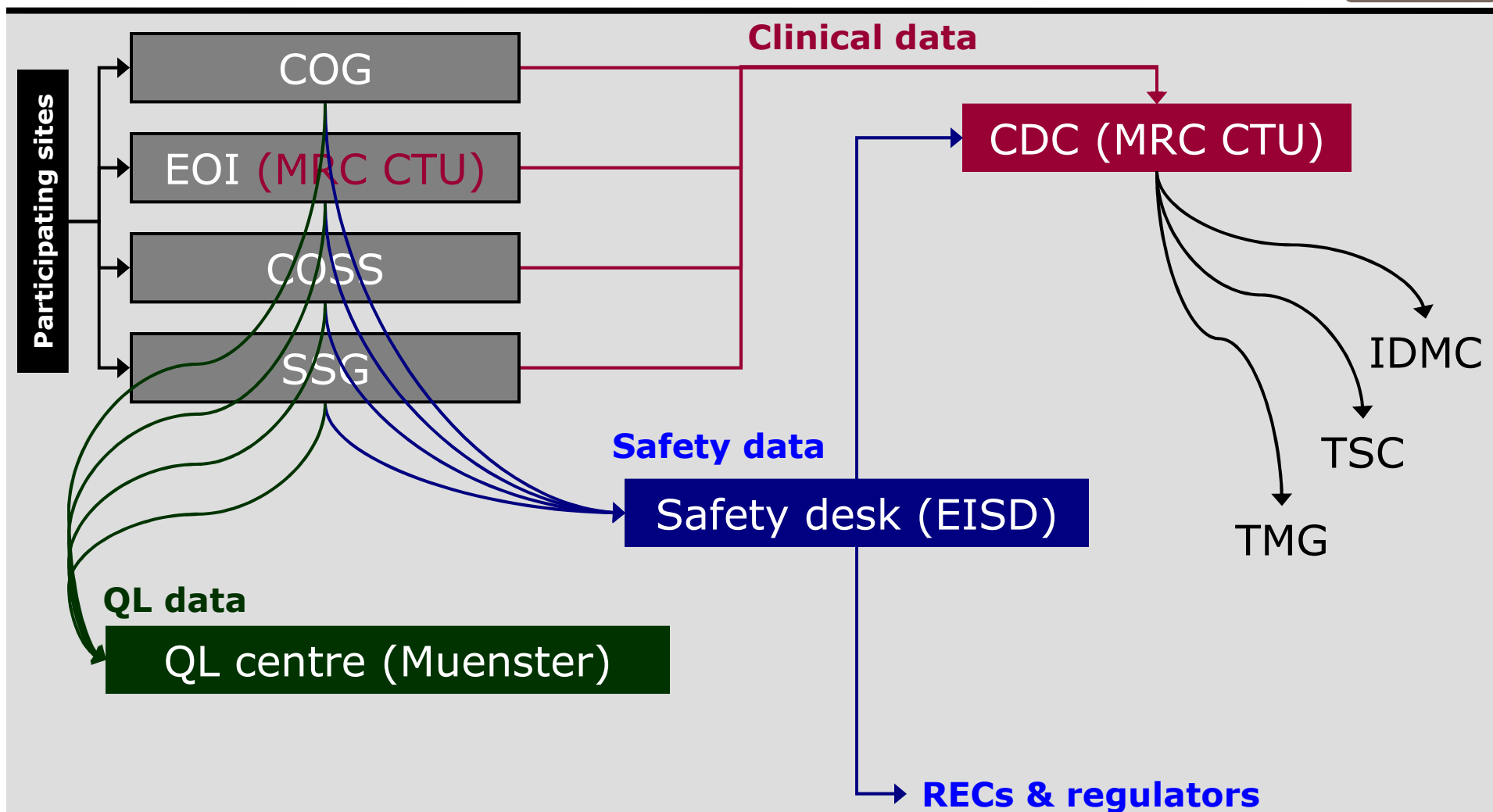
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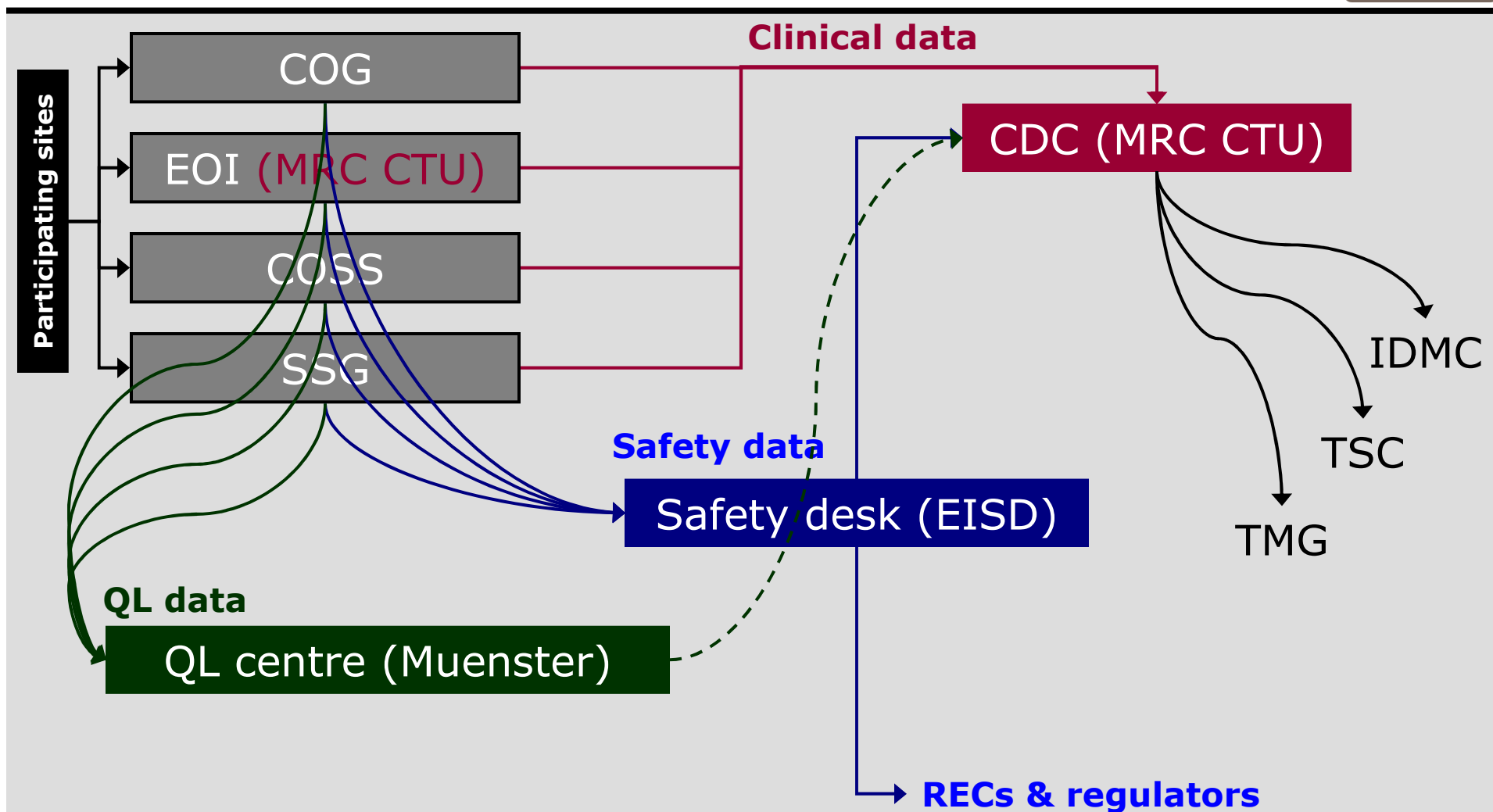
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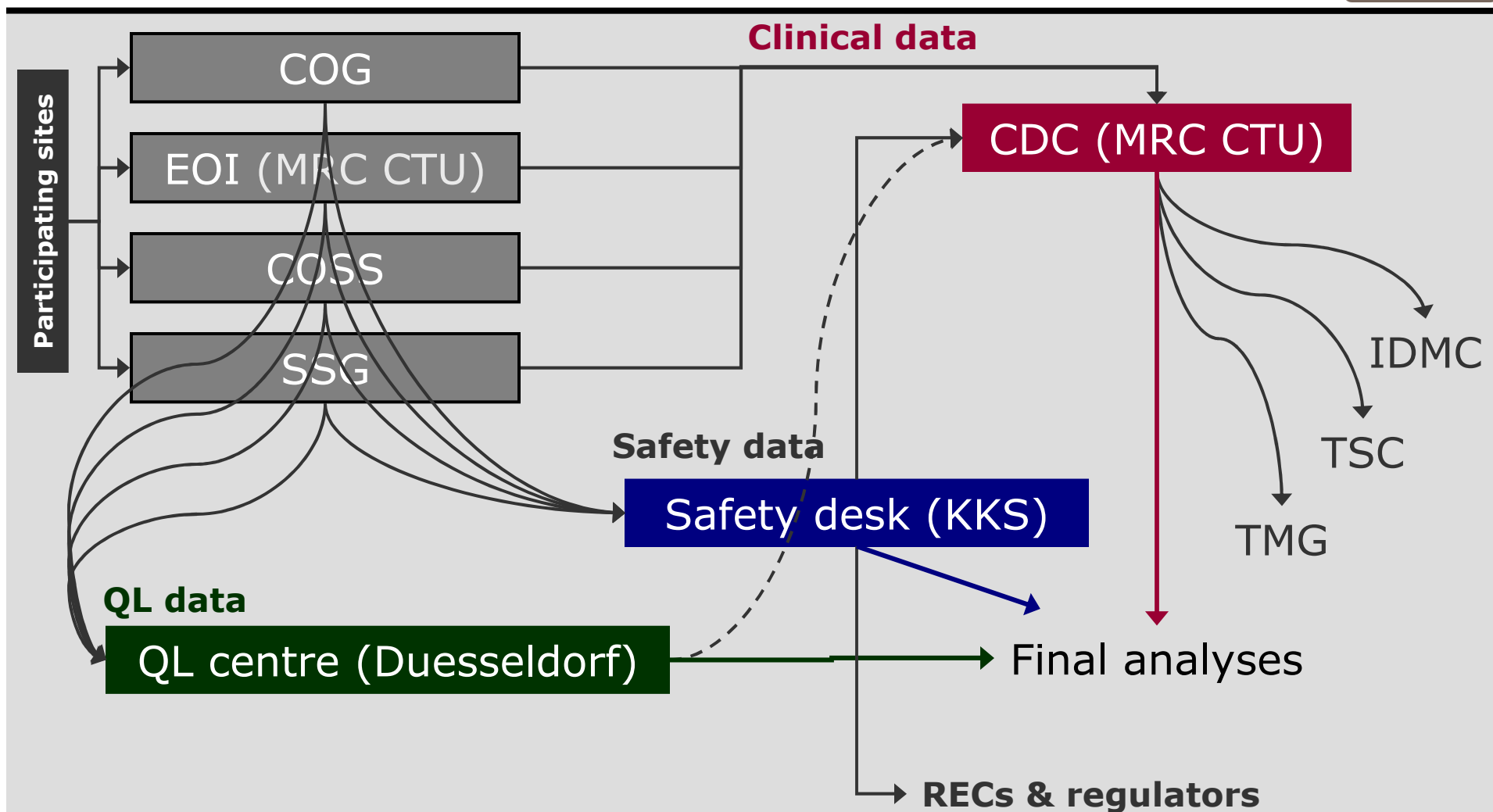
EURAMOS dataflow



EURAMOS dataflow



EURAMOS dataflow



EURAMOS-1 infrastructure

Practical issues: common data and CDC role

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Data Monitoring Committees

- Many names used for this committee
 - 46 names in 662 trials
- Recommend “DMC”
 - Standardisation helpful
 - Short
 - Doesn't emphasise only some roles (eg safety)
 - ICH GCP

DAMOCLES study group

BSU, Cambridge

David Spiegelhalter

CSM, Oxford

Doug Altman

CTU, London

Abdel Babiker

Janet Darbyshire

Mahesh Parmar

Matthew Sydes

HRSU, Aberdeen

Marion Campbell

Adrian Grant

Sharon McLeer

Anne Walker

Sheila Wallace

LSHTM, London

Felicity Clemens

Diana Elbourne

Stuart Pocock

DAMOCLES project aims

- Examine DMC processes and identify how “right” decisions are made
- Role of DMCs
- Structure and organisation
- Information available to DMCs
- Decision-making and reporting in DMCs

DAMOCLES methodology

- 1 Systematic review of literature on DMCs
- 2 Systematic review of small group processes relevant to DMCs
- 3-6 Surveys:
 - DMC use in published RCT reports
 - DMC use in recent RCTs
 - DMC use in ongoing RCTs
 - DMC policies of relevant organisations
- 7 Case studies DMCs
- 8 Interviews with experienced DMC members

Some DAMOCLES results: which trials need IDMCs?

- Efficacy of a new intervention
- Efficacy in a new indication
- High-risk treatments
- Treatments with possible safety issues
- Long-term follow-up period

Some DAMOCLES results: responsibilities of the DMC

- Patients in the trial
- Future patients to be enrolled in the trial
- Future patients in target population treated after the trial
- Society in general
- Principal investigators
- Steering committee
- Sponsor

Some DAMOCLES results: primary role of DMC

- Review interim analyses of outcome data
- Monitor trial for safety
- Monitor trial for early convincing benefit
- Protect trial subjects
- Ensure patients' risks are reasonable
- Protect participant safety and trial integrity
- Protect patients in the trial and other patients with the disease in question

Some DAMOCLES results: before or early in the trial

- Members' input into the protocol unclear
- DMC should meet very early to discuss the trial and possible difficult scenarios

Some DAMOCLES results: size and composition

- Median size 4, 3-8
 - literature review 3-20+
- Size likely to affect decision-making process
- Size should not exceed 6; odd number useful
- Appropriate range of membership

Some DAMOCLES results: the chair

- Appointment of chair is crucial
- Often an eminent person in the field
- The chair can have a big impact on decision making
- Decisions are of better quality if the chair
 - facilitates rather than directs
 - is impartial

Some DAMOCLES results: organisation of meetings

- Specified minimum frequency of meetings
- Face-to-face meetings are preferred
- Teleconferences can be useful especially if members are in different countries

Some DAMOCLES results: 3 models for DMCs

1. All members are completely independent and the statistician is independent
2. Investigators can attend the meeting but decisions are taken by independent members. Open and closed sessions are used to include the appropriate people at different stages of the meeting
3. There are independent members but non-independent members take part in the decision-making

Some results: relationships

- Advisory rather than executive is preferable
- Chair reports to PI and/or TSC
- Planned relationships should be carefully defined in advance
- Suggested arrangements in case of disagreement between the DMC and the TSC

Some results: decision-making

- Options for DMC
 - DMC should be aware of the implications of the decision to stop at each stage of the trial
 - Voting after a full discussion
 - Unanimity where possible
 - The role of statistical “stopping rules”

DAMOCLES publications

1. The DAMOCLES study group. **Issues in data monitoring and interim analysis of trials. Health Technology Assessment monograph series** 2005, 9(7)
2. The DAMOCLES study group. **A proposed charter for clinical trial Data Monitoring Committees: helping them to do their job well. Lancet** 2005, 365: 711-722
3. Sydes MR, Altman DG, Babiker AB, Parmar MKB, Spiegelhalter DJ, DAMOCLES Group. **Reported use of data monitoring committees in the main published reports of randomised controlled trials: a cross-sectional study. Clinical Trials**; 2004, 1(1): 48-59
4. Sydes MR, Spiegelhalter DJ, Altman DG, Babiker AB, Parmar MKB, DAMOCLES Group. **Systematic qualitative review of the literature on data monitoring committees for randomized controlled trials. Clinical Trials**; 2004, 1(1): 60-79
5. Walker AE, McLeer SK, DAMOCLES group. **Small group processes relevant to data monitoring committees: an overview of reviews. Clinical Trials**; 2004, 1(3): 282-296
6. Clemens F, Elbourne D, Darbyshire J, Pocock S, DAMOCLES group. **Data monitoring in randomised controlled trials: surveys of recent practice and policies. Clinical Trials** 2005; 2(1): 22-32

Bringing it together

- Lack of guidance or standard operating procedures for DMCs
 - Charter
- Clarity from variety
- Systematic and transparent approach
 - Structure
 - Operation
 - Policy
 - Process
- Should be set out before start of trial
- Highlight areas which may not be often currently

What can Charters do for us?

- Roles
- Responsibilities
- Process – what and how
- Consistency and structure
- Difficult situations

Implementation

- Ideally before or at first DMC meeting
 - Can be set up once trial is under way
- Early agreement on potential difficult issues
- Should be drawn up with input from
 - Trial investigators (TMG)
 - DMC members
 - Sponsor, funder, executive body (TSC)
- All should agree on the Charter contents
- Iterative process – expect agreement on most areas

DMC charter

EURAMOS 1 INDEPENDENT DATA MONITORING COMMITTEE CHARTER	
CONTENT	EURAMOS APPLICATION
1. Introduction	
Name (and sponsor's ID) of trial plus ISRCTN and/or EUDRACT number	<i>EURAMOS 1</i> : A randomized trial of the European and American Osteosarcoma Study Group to optimize treatment strategies for resectable osteosarcoma based on histological response to pre-operative chemotherapy (ISRCTN67613327, EUDRACT 2004-000242-20)
Objectives of trial, including interventions being investigated	The trial objectives are to evaluate: <ol style="list-style-type: none"> 1) Whether the addition of ifosfamide and etoposide to post-operative chemotherapy with cisplatin, doxorubicin and methotrexate improves the event-free survival of patients with resectable osteosarcoma and a poor histological response to 10 weeks of pre-operative chemotherapy. 2) Whether the addition of interferon-α as a maintenance therapy after post-operative chemotherapy with cisplatin, doxorubicin and methotrexate improves the event-free survival and overall survival of patients with resectable osteosarcoma and a good histological response to 10 weeks of pre-operative chemotherapy. 3) To investigate the short and long term toxicity of therapy for each regimen 4) To investigate whether biological or clinical correlates to histological response and outcome can be identified 5) To establish whether this international co-operation in clinical trials for osteosarcoma is feasible 6) To examine the outcome of the entire cohort of patients (See Figure 1).
Outline of scope of charter	The purpose of this document is to describe the roles and responsibilities of the Independent Data Monitoring Committee (IDMC) for the <i>EURAMOS 1</i> trial, including the timing of meetings, methods of providing information to and from the IDMC, frequency and format of meetings, statistical issues and relationships with other committees.
2. Roles and responsibilities	
A broad statement of the aims of the committee	To safeguard the interests of trial's participants, potential participants, investigators and sponsor; to assess the safety and efficacy of the trial's interventions, and to monitor the trial's overall conduct and ethics thereby protecting its validity and credibility.
Terms of reference	The IDMC should review the progress and accruing data of this trial and provide advice on the conduct of the trial to the Trial Steering Committee (TSC).
Specific roles of IDMC	To provide interim review of the trial's progress by: <ul style="list-style-type: none"> ▪ assessing data quality, including completeness (thereby encouraging collection of high quality data)

Aims of IDMC

A broad statement of the aims of the committee

To safeguard the interests of trial's participants, potential participants, investigators and sponsor; to assess the safety and efficacy of the trial's interventions, and to monitor the trial's overall conduct and ethics thereby protecting its validity and credibility.

Roles & responsibilities

Specific roles of the committee

To provide interim review of the trial's progress by:

assessing data quality, including completeness (thereby encouraging collection of high quality data)

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monitoring evidence for treatment differences in the main efficacy and safety outcome measures – and thus recommending action when/whether the main trial question has been answered

Roles & responsibilities

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Specific roles of the committee

monitoring planned sample size with regards (i) *a priori* assumptions about the control arm outcome and (ii) emerging differences in clinical relevant subgroups

suggest additional data analyses

assessing the impact and relevance of any external evidence provided

monitoring compliance with previous IDMC recommendations

considering the ethics of the trial

The IDMC should **not** have a role in increasing or decreasing the planned sample size as it is not blind to the current results of the trial.

Composition

The chair, how they are chosen and the chair's role.

The chair will be chosen by the IDMC members at the first meeting.

The chair is expected to facilitate and summarize discussions.

Composition

The responsibilities of the Chief Investigators and other members of the TMG

The Chief Investigator (CIs) ... may be asked, and should be available, to attend open sessions of the IDMC meeting.

The other TMG members will not usually be expected to attend but can attend open sessions when necessary

Relationships

Clarification of whether the IDMC are advisory (make recommendations) or executive (make decisions)

The IDMC are advisory to the TSC.

The TSC is the executive body for the trial. It contains representatives of the investigators and independent members.

Relationships

The need for IDMC members to disclose information about any competing interests

Competing interests should be disclosed. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility. Most competing interests are acceptable if disclosed.

IDMC members should not use interim results to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products.

Organisation of meetings

Whether meetings will be face-to-face or by teleconference

The first meeting should be face-to-face. It is recommended that the IDMC meet face-to-face at least once a year for subsequent meetings, with teleconference as a second option. At least one of the CIs should try to attend in person if the IDMC request their presence.

Trial documentation

Will the IDMC be blinded to the treatment allocation?

The IDMC will not be blinded to the identity of the treatment arms.

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Who will see the accumulating data and interim analysis?

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IDMC members must not share confidential information with anyone outside the IDMC, including the CIs.

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What decisions / recommendations will be open to the IDMC

The possible recommendations are numerous and could include:-

- No action needed, trial continues as planned
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- Stopping recruitment within a subgroup
- Extension of recruitment/follow-up
- Advising on or proposing protocol changes

Decision making

The role of formal statistical methods, specifically which methods will be used and whether they will be used as guidelines or rules

A recommendation to discontinue recruitment, in all patients or in selected subgroups, will be made only if the result is likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community.

The Haybittle-Peto stopping rule will be adopted for this trial... Consideration will be given to stopping the trial for good or poor responders if the p-value for the analysis of EFS is below 0.001.

...

Decision making

//cont

The role of formal statistical methods, specifically which methods will be used and whether they will be used as guidelines or rules

If any toxic death occurs that is attributable to interferon- α , the IDMC and TSC will be consulted within 7 days with a view to discontinuing this arm. If, at interim analysis, $> 25\%$ of patients who started interferon- α have subsequently ceased treatment for any reason other than disease progression, relapse or death, the TMG will discuss whether to discontinue this arm with the IDMC and TSC.

Decision making

How decisions or recommendations will be reached within the IDMC

The role of the chair should be to summarize discussions and encourage consensus. In each area of discussion the chair should give their own opinion last.

Every effort should be made for the IDMC to reach a consensus. If the IDMC cannot achieve consensus, a vote should be taken...

Decision making

When the IDMC is quorate for decision-making

Effort should be made for all members to attend. The CDC trial team will try to ensure that a date is chosen to enable this. Members who cannot attend in person should be encouraged to attend by teleconference.

If, at short notice, an IDMC member cannot attend at all then the IDMC may still meet if at least one statistician and two clinicians will be present...

If an IDMC member is unable to attend two consecutive meetings, their membership will be reviewed.

Reporting

To whom the IDMC will communicate the decisions/recommendations that are reached

The IDMC will report its recommendations in writing to the TSC. This should be copied to the CDC trial statistician (or trial manager) and should be sent via the CDC prior to the TSC meetings.

A copy of the report will be sent to all the trial statisticians.

If the trial is to continue largely unchanged then it is often useful for the report from the IDMC to include a summary paragraph suitable for trial promotion purposes

Reporting

What will be done in the instances of disagreement between the IDMC and the body to which they report

If the IDMC has serious problems or concerns with the TSC decision, a meeting of these groups should be held....

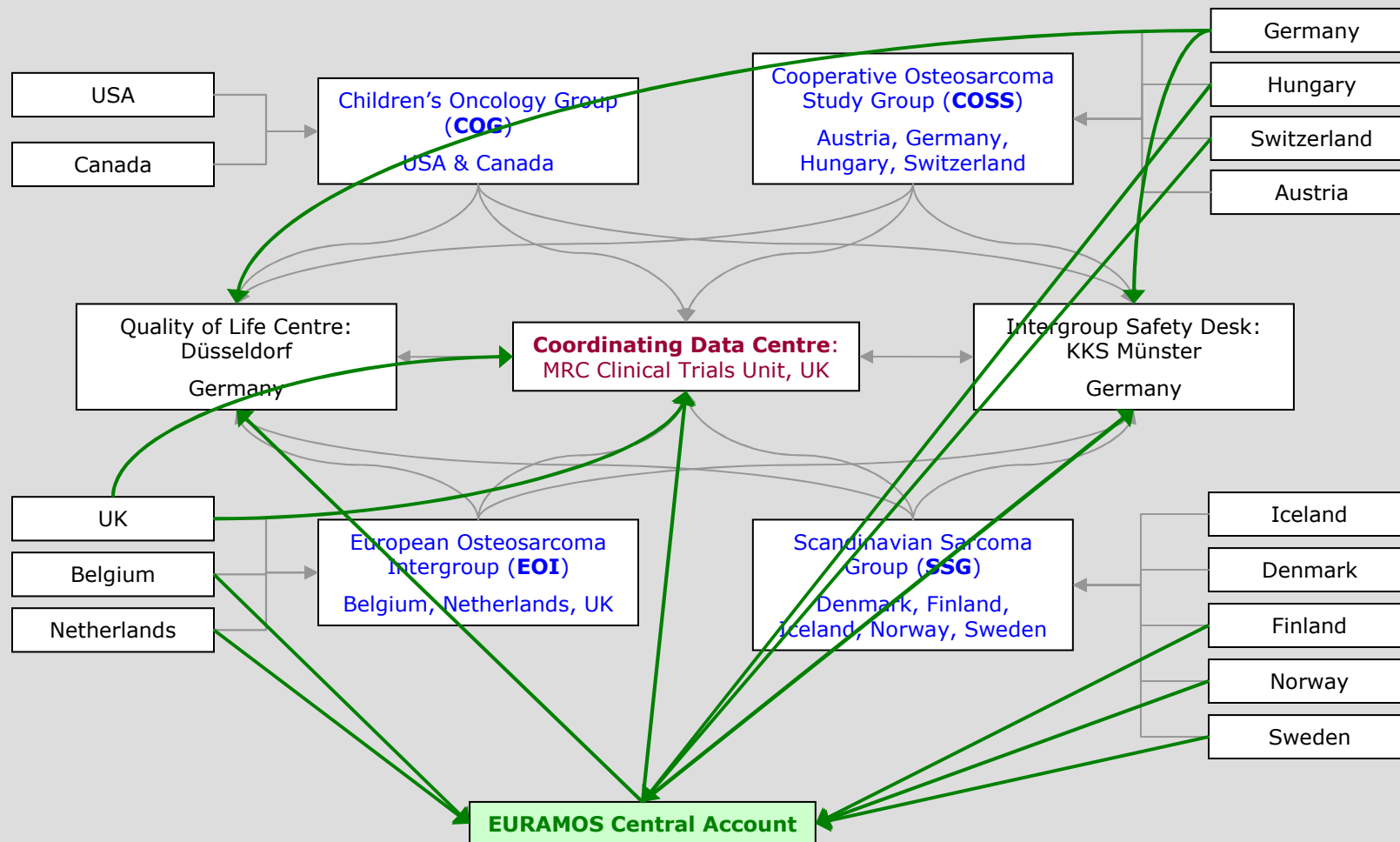
The meeting should be chaired by a senior member of CDC staff or an external expert who is not directly involved with the trial.

After the trial

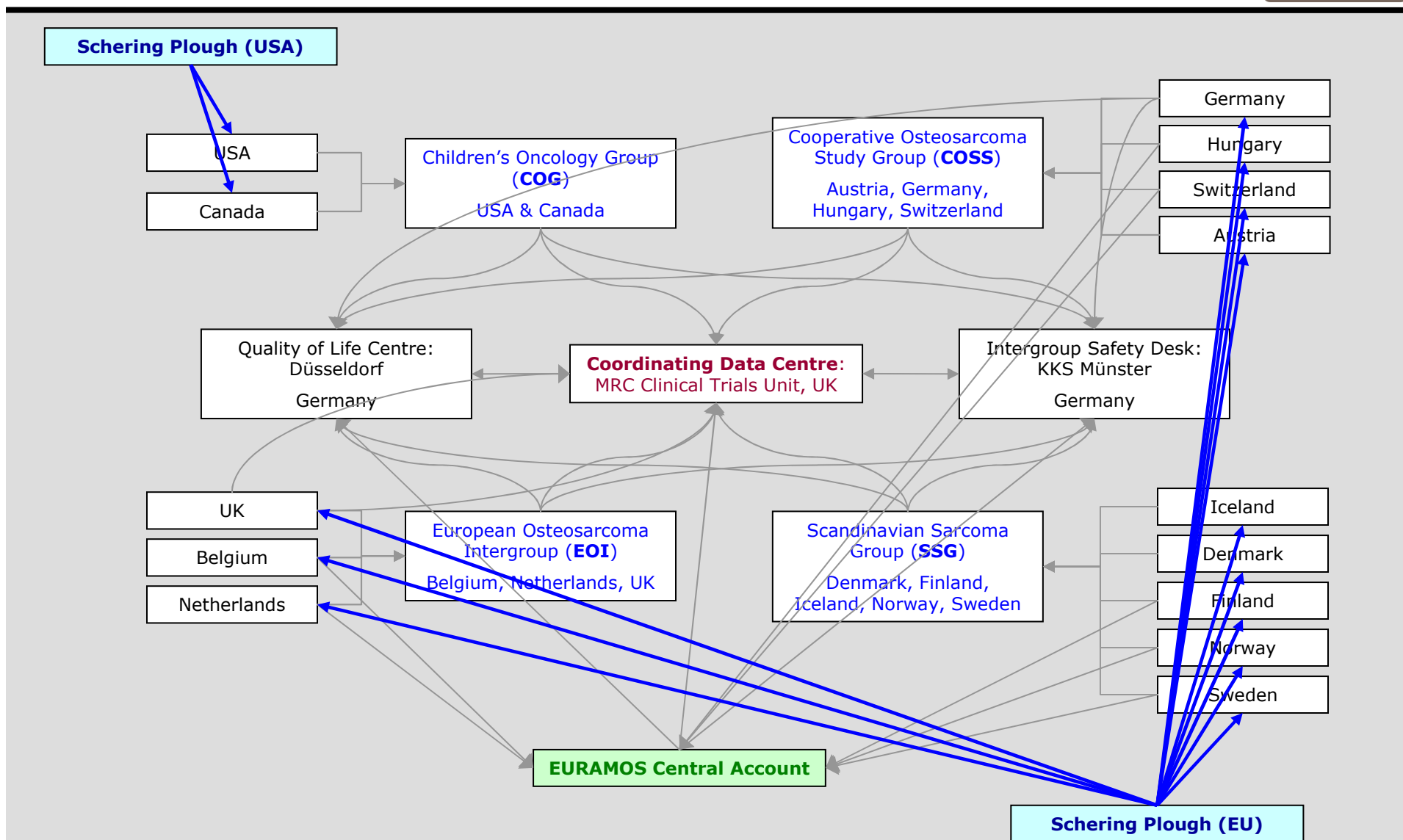
The information about the IDMC that will be included in published trial reports

IDMC members will be named and their affiliations listed (unless they specifically ask not to be) in the primary published report. A brief summary of the timings and conclusions of IDMC meetings should be included in the body of this paper.

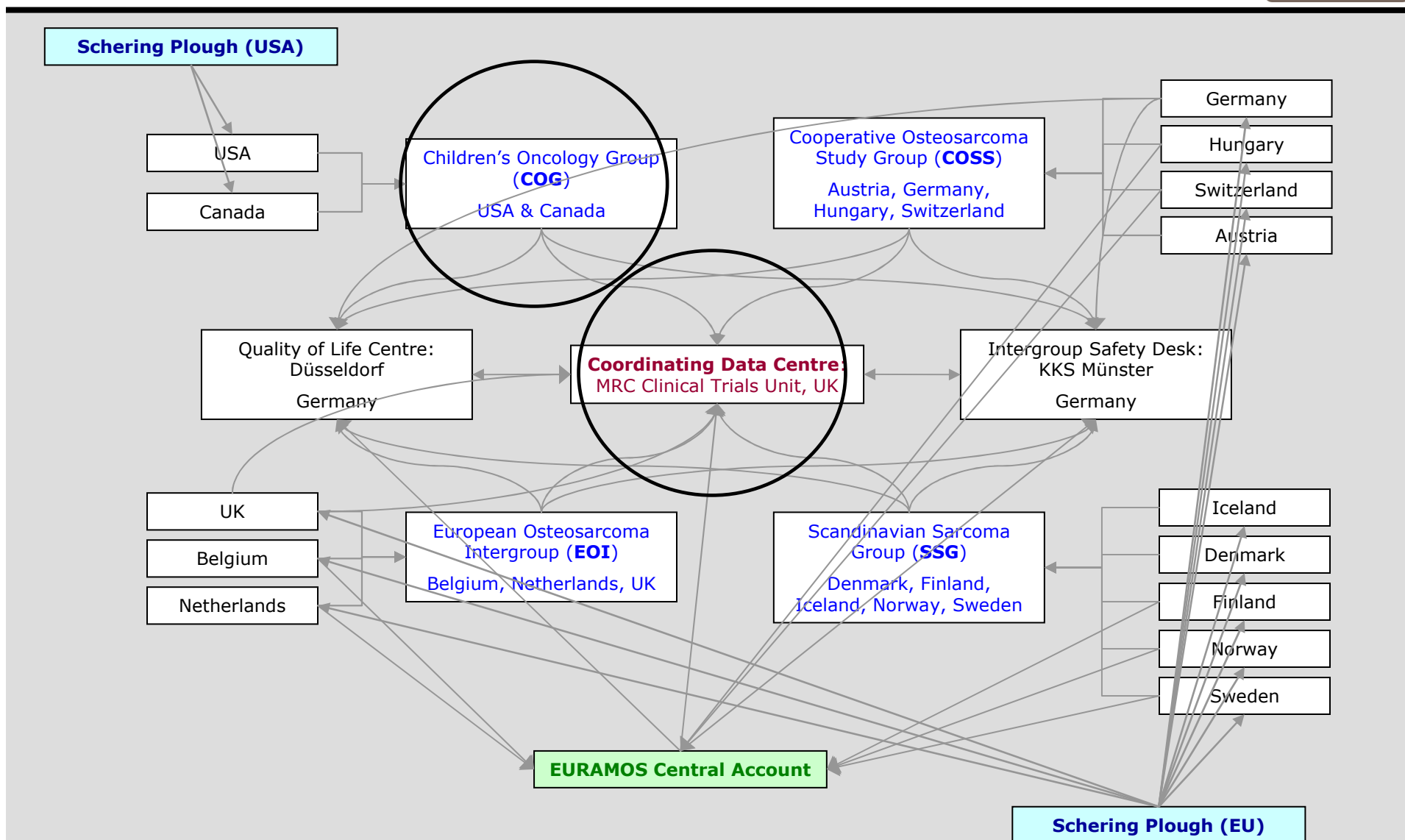
EURAMOS groups + structure



EURAMOS groups + structure



EURAMOS groups + structure



Sponsorship and agreements

- Intergroups as collaborations
 - No legal existence
- Planned for Sponsor in each country
 - Legal entity in place
- Contract between SP and who?
- Choosing one Sponsor for EU
- Confirming one Sponsor
 - Agreements
- Development of agreements

Major agreements & contracts

