UNIVERSITY OF BIRMINGHAM

Clinical Trials in Europe

The Framework and Perspective

Professor Pam Kearns

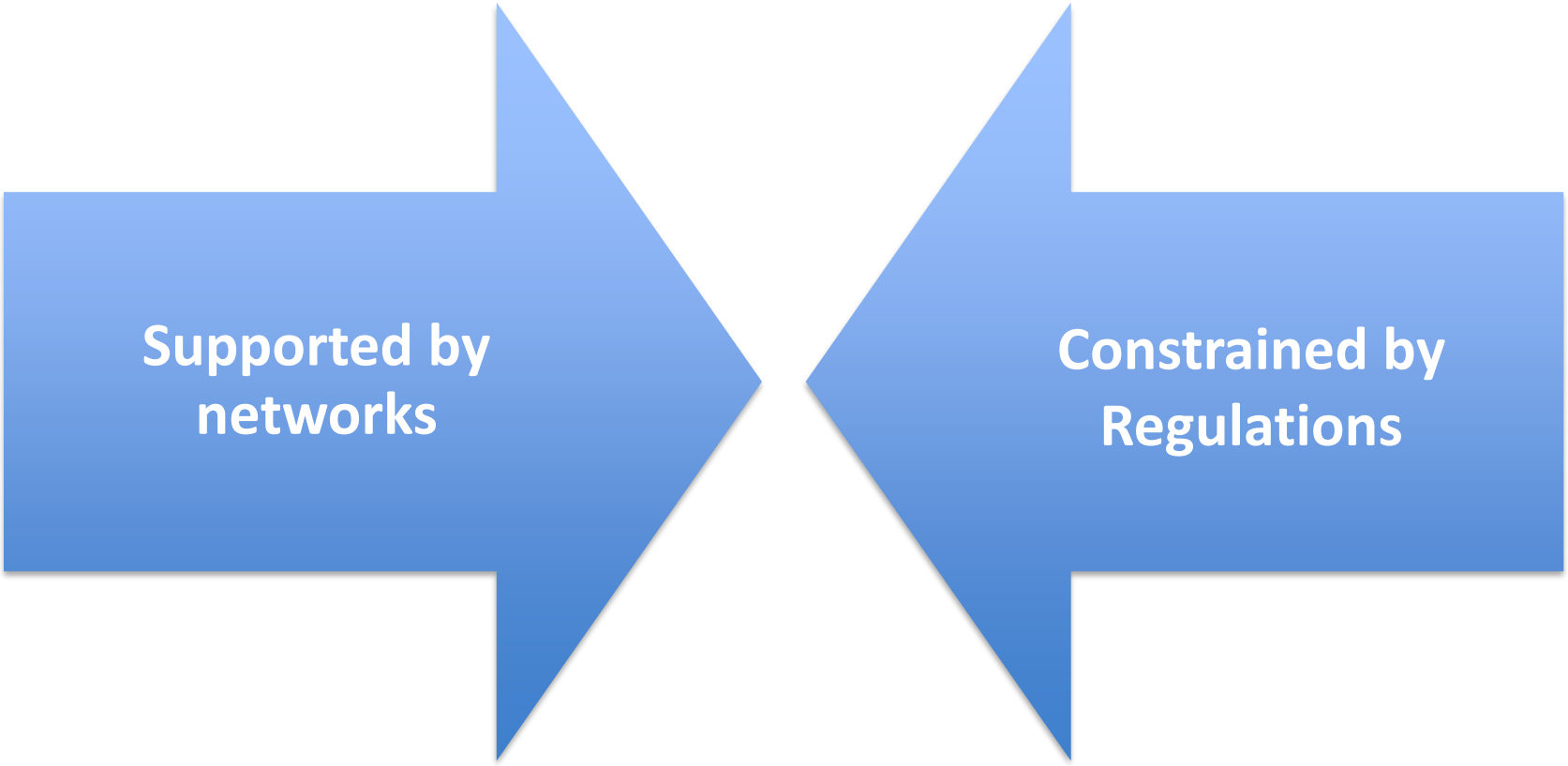
Director of The Cancer Research UK Clinical Trials Unit
University of Birmingham

Paediatric Oncology Trials

- Rare diseases
  - Stratified into sub-groups
    - Pathological sub-types
    - Disease Stage
    - Predictive factors /biomarkers
      - Cytogenetics, early tumour response
    - Molecular sub-groups for targeted drugs

International Collaboration is central to success for paediatric oncology research

Paediatric Oncology Trials in Europe



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European Clinical Trial Groups

- SIOPEL (SIOPE-Epithelial Liver Tumour Study Group) — Liver Tumours
- Myelodysplasia — EWOG-MDS
- SIOPEN (SIOP Europe Neuroblastoma Group) — Neuroblastoma
- New Anticancer Agents — ITCC (Innovative Therapies for Children with Cancer)
- EICNHL (European Inter-group cooperation on childhood and adolescent Non Hodgkin) — Non-Hodgkin Lymphoma
- Osteosarcoma — EURAMOS
- SIOP-RTSG (SIOP Wilms Tumour) — Renal Tumours
- Soft Tissue Sarcomas — CWS (Cooperative Weichteilsarkom Studiengruppe or Cooperative Soft Tissue Sarcoma StudyGroup)
- EpSSG (European Paediatric Soft Tissue Sarcoma Study Group) — Soft Tissue Sarcomas
- Stem Cell Transplantation — EBMT (European Group for bone marrow and stem cell transplantationPaediatric Working Party)
- PanCare — Survivorship and Late Effects
- Very Rare Pediatric Tumours — EXPeRT (European Cooperative Study Group on Paediatric Rare Tumours)
- EURBG (European RetinoBlastoma Group) — Retinoblastoma
- SIOPE Brain tumour group — Brain Tumour
- Ewing's Tumour — EURO- E.W.I.N.G.
- Germ Cell Tumours — Germ Cell Tumours
- Hodgkin's Lymphoma — EHL (European Hodgkins Consortium, EuroNet-PHL)
- Histiocyte Society — Langerhans Cell Histiocytosis
- Leukemias and Lymphomas — I-BFM (The International BFM Study Group)

https://www.siope.eu/

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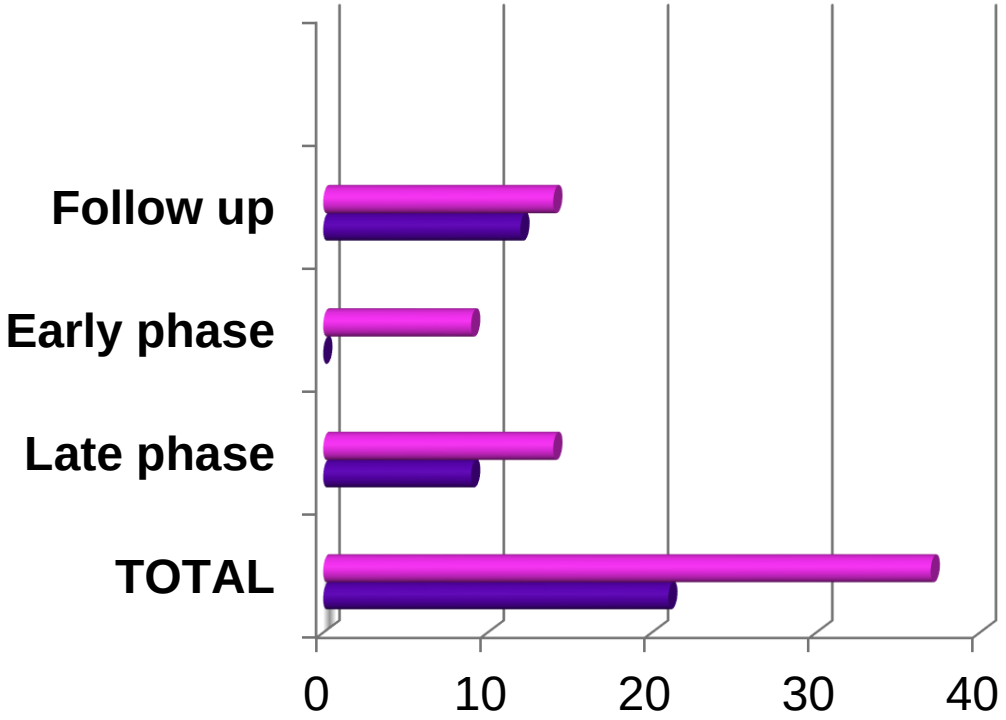
UK CHILDREN'S CANCER TRIALS TEAM
Close partnership with the NCRI CCL CSG



almost all childhood cancer trials are international

Euro Ewing 2012

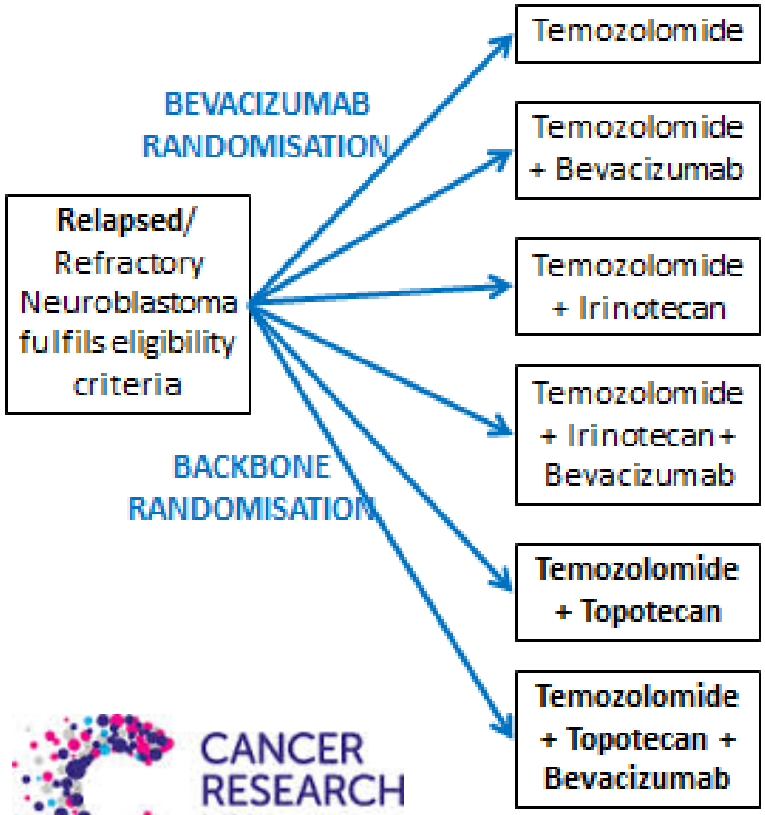
Phase RCT incorporating Bayesian design

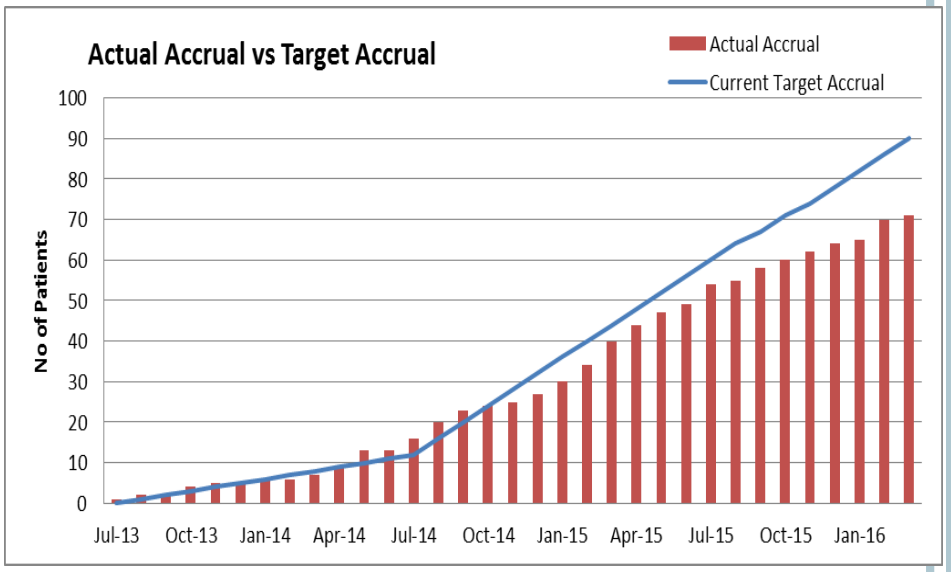
Multi-arm global programme

MyeChild 01

International Phase III RCT with an embedded dose finding study / Pharma Collaborative trial

BEACON-Neuroblastoma



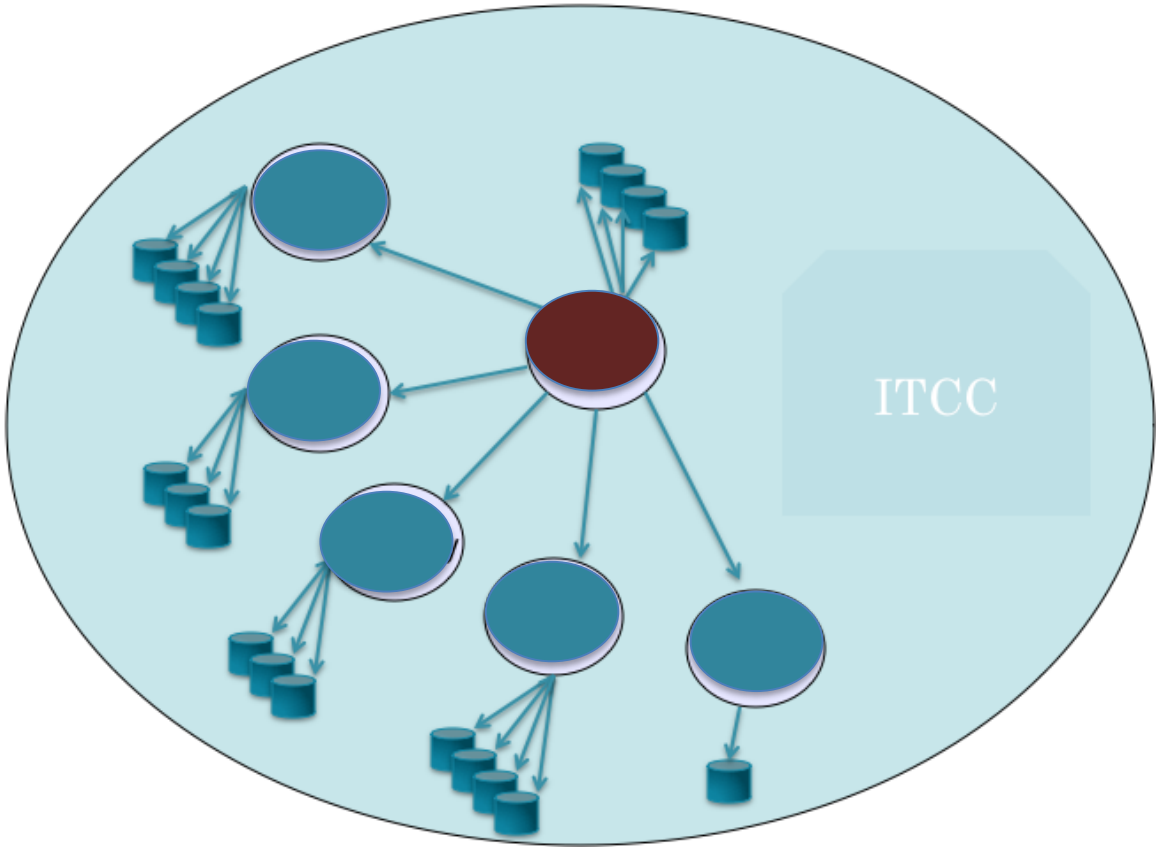


SPONSORSHIP MODEL FOR ACADEMIA-LED TRIALS WITHIN ITCC

International Sponsoring Centre

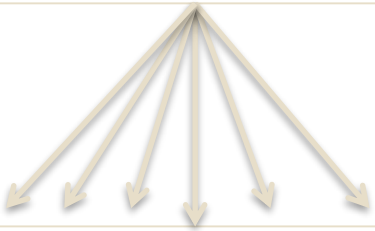
National Co-ordinating Centres

sites

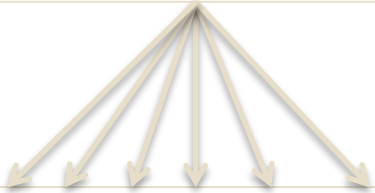


BEACON-Neuroblastoma

International Sponsor
University of Birmingham CRCTU
CI Lucas Moreno



8 National Coordinating Centres
National coordinating investigator identified in each country

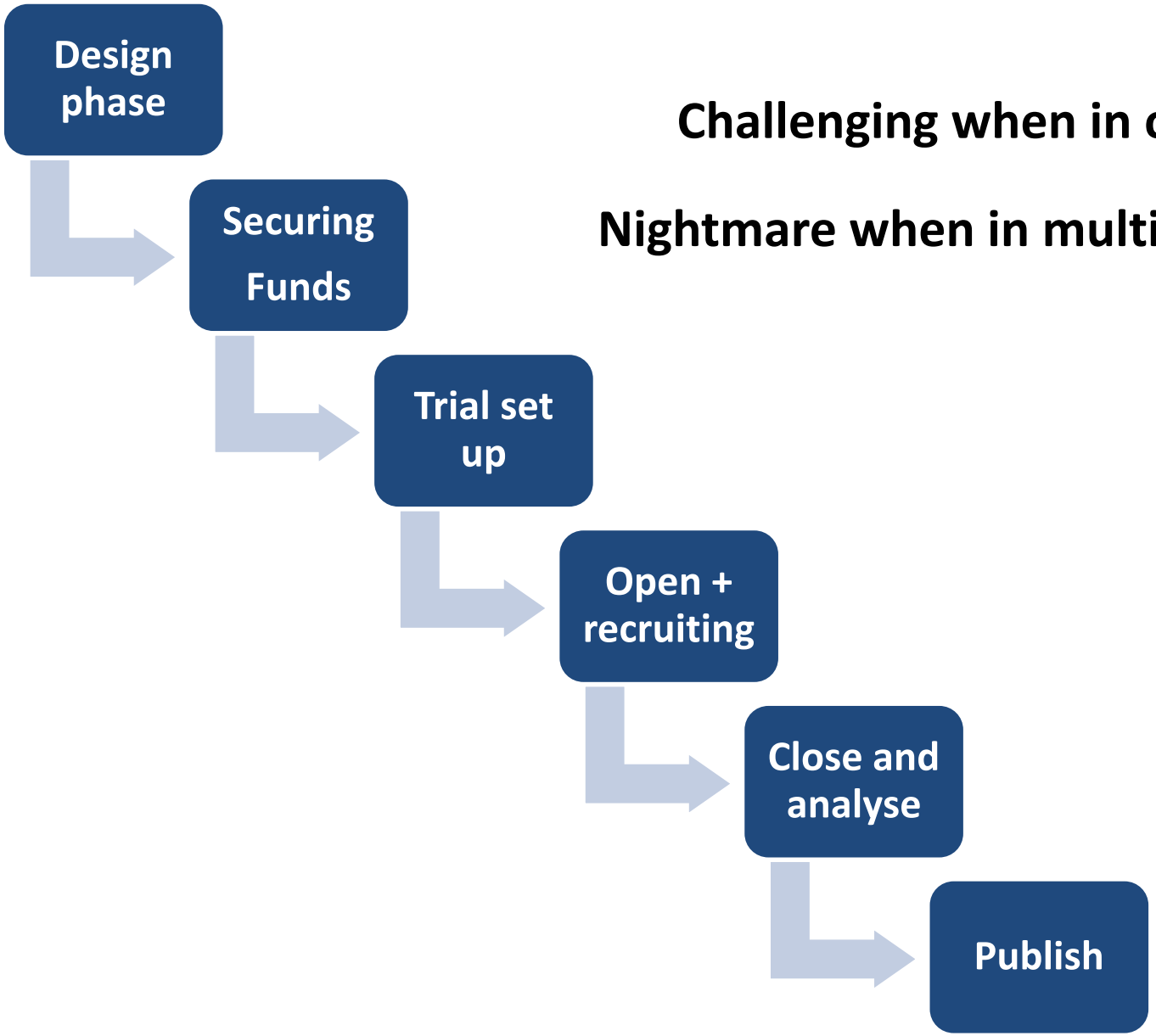


20-26 Sites
Principal investigator in each site

- Regulatory submissions
- Initiation of sites
- Monitoring
- Funding

Ruth Ladenstein - Austria
Hervé Rubie – France
Aurora Castellano – Italy
Victoria Castel - Spain
Jochen Rößler - Germany
Huib Caron – Netherlands
Karsten Nysom - Denmark

What steps are involved in delivering a trial?



Challenging when in one country

Nightmare when in multiple countries!

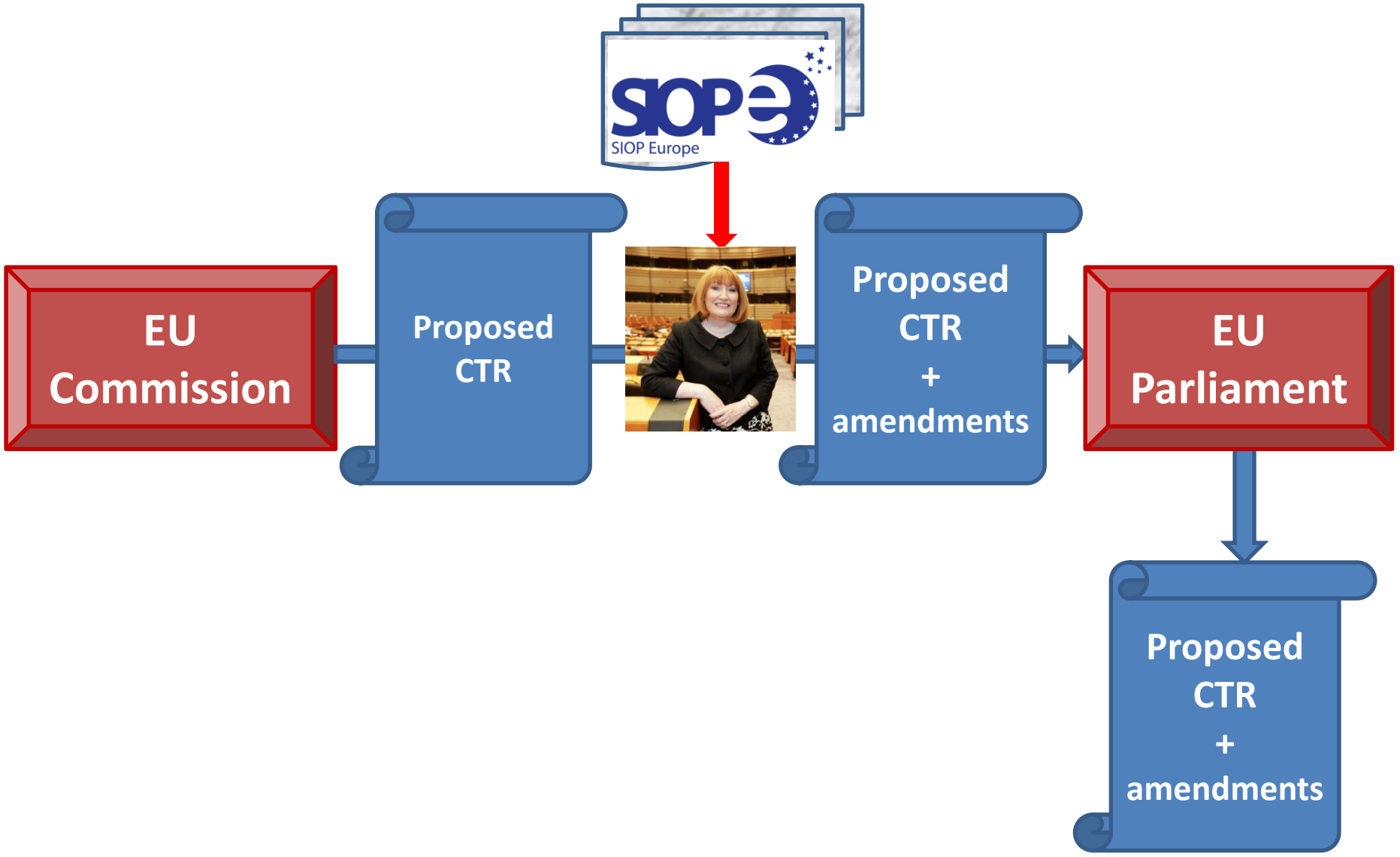
EU Clinical Trial Directive

- Intentions
  - to ensure compliance with GCP
    - Protect the rights of patients and integrity of trial data
  - Harmonise trial delivery across the EU
- Unintended consequences
  - Increased bureaucracy
  - Discrepancies in national interpretations
  - Increased costs
  - Decrease in numbers of academic sponsored clinical trials

Universally disliked legislation

New EU Clinical Trial Regulation

The Regulation's Journey













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SIOPE
@SIOPEurope

Follow

#SIOPE soon discussing the #CTR @EFGCP Workshop on 'Indemnity Schemes for Clinical Trials' bit.ly/1cvVCgG

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Go Back

The EU Clinical Trials Regulation: SIOPE position

19 Sep 2013

THE LANCET Oncology

Volume 14, Issue 6, May 2013, Pages 454–455

Comment

The need for proportionate regulation of clinical trials

Pamela Kearns[a]

THE LANCET Oncology

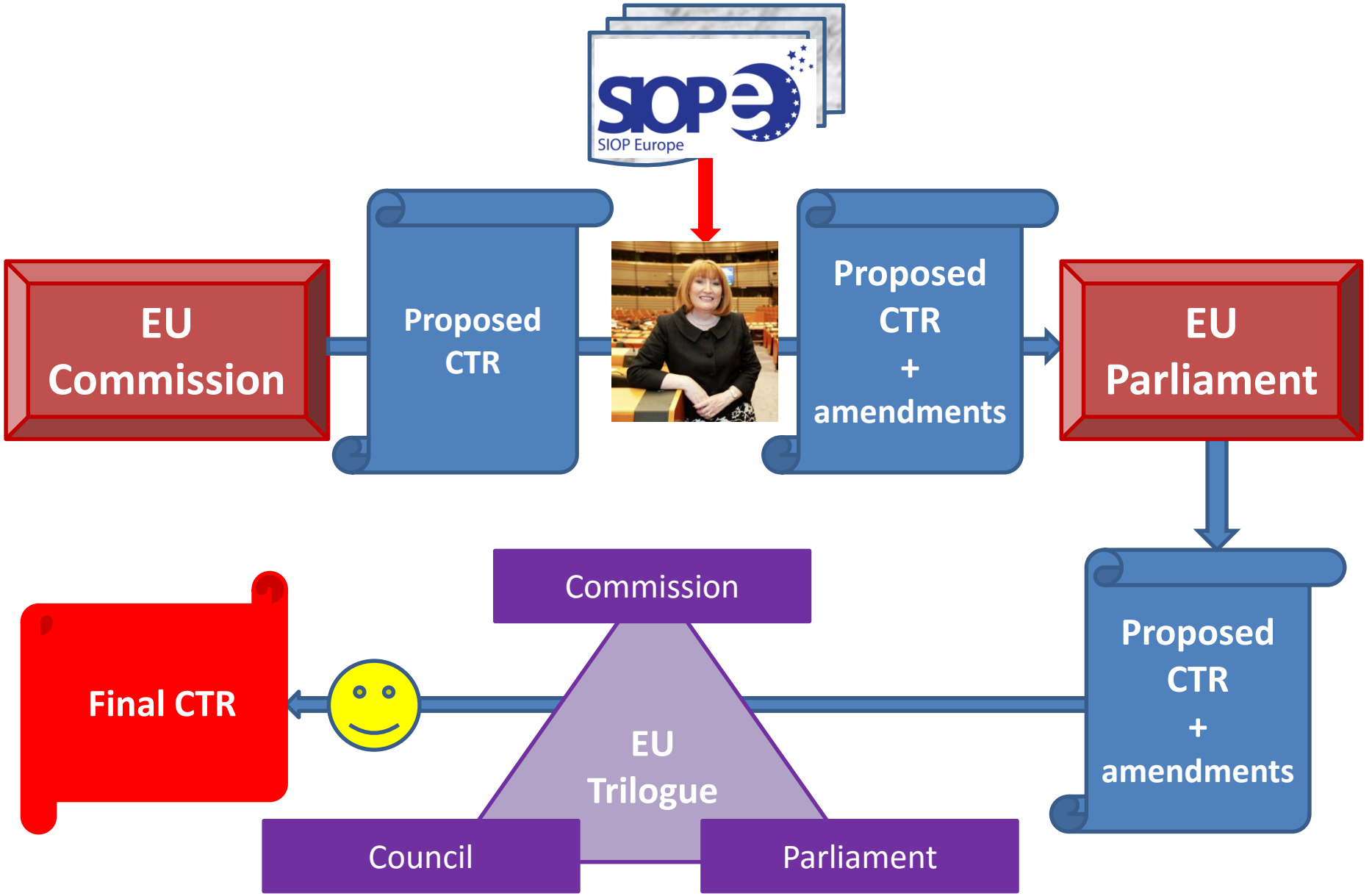
/olume 14, Issue 6, May 2013, Pages 453–454

Comment

Regulating clinical trials in Europe

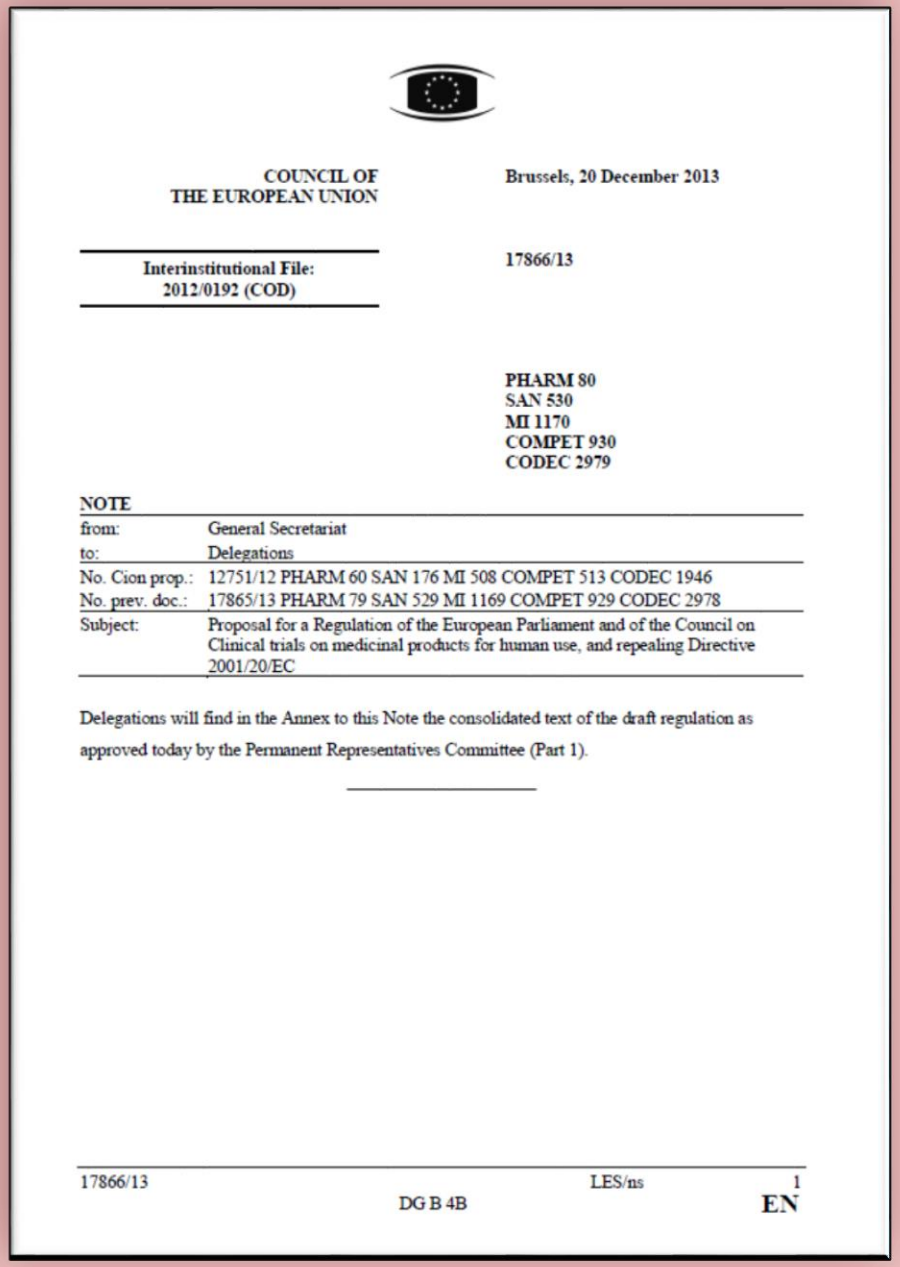
Glenis Willmott[a]

The Regulation's Journey



Clinical Trial Regulation

Approved by Trilogue 20/12/2013
Implementation expected 2018



COUNCIL OF
THE EUROPEAN UNION

Brussels, 20 December 2013

Interinstitutional File:
2012/0192 (COD)

17866/13

PHARM 80
SAN 530
MI 1170
COMPET 930
CODEC 2979

NOTE

from:	General Secretariat
to:	Delegations
No. Cion prop.:	12751/12 PHARM 60 SAN 176 MI 508 COMPET 513 CODEC 1946
No. prev. doc.:	17865/13 PHARM 79 SAN 529 MI 1169 COMPET 929 CODEC 2978
Subject:	Proposal for a Regulation of the European Parliament and of the Council on Clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

Delegations will find in the Annex to this Note the consolidated text of the draft regulation as approved today by the Permanent Representatives Committee (Part 1).

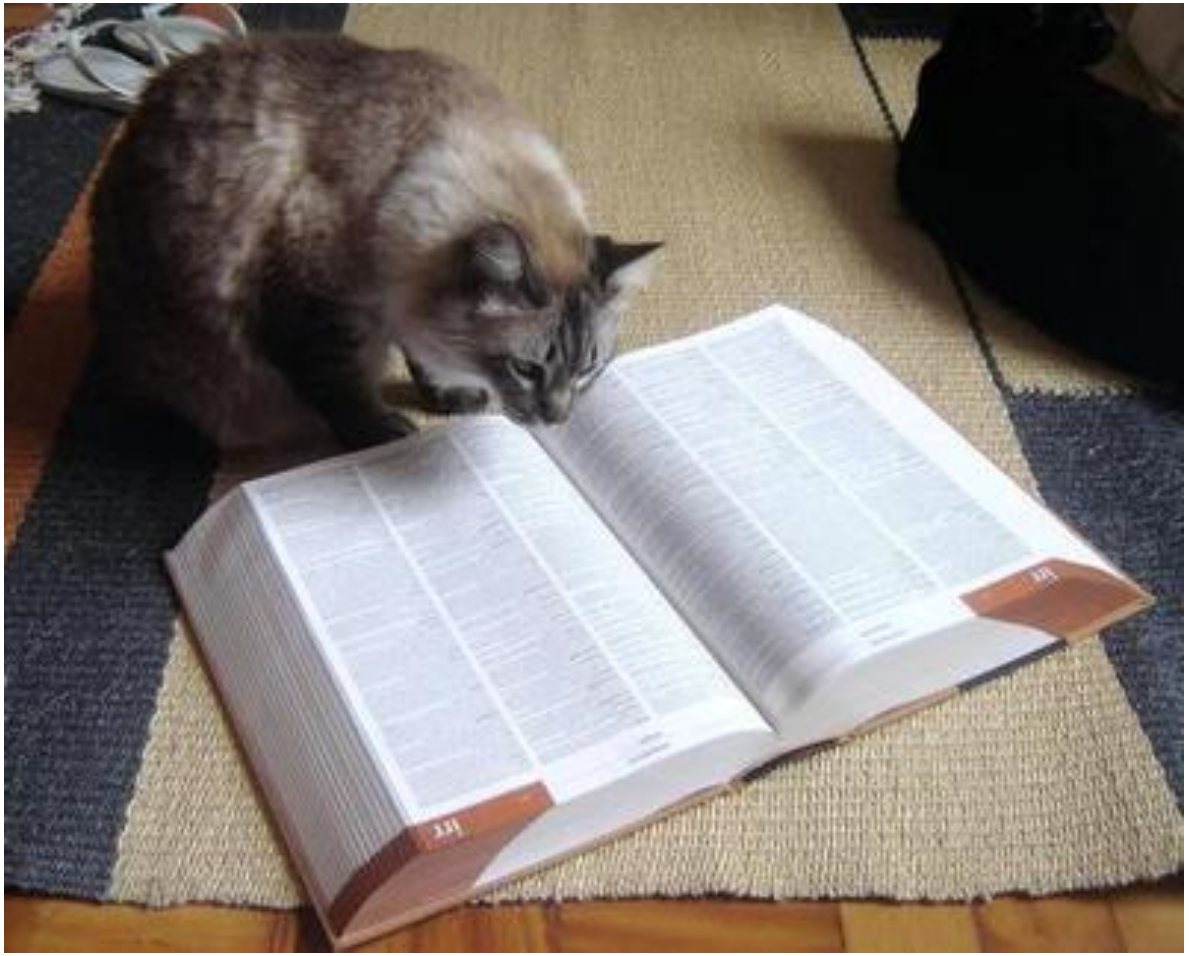
17866/13 LES/ns 1
DG B 4B EN

66 'Principles'

92 Articles

4 Annexes

Will the new Clinical Trials Regulation benefit Paediatric Oncology?



The New Clinical Trials Regulation aims to encourage non-commercial trials

- ***(10c) Experience with Directive 2001/20/EC has also shown that a large part of clinical trials are conducted by non-commercial sponsors. Non-commercial sponsors frequently rely on funding which partly or entirely comes from the public funds or charities. In order to maximize the use of their valuable contribution and to further stimulate their research but without any discrimination towards the quality of trials, measures should be taken by Member States to encourage trials conducted by non-commercial sponsors.***

Sponsors and Co-Sponsors

(42) In order to ensure clear responsibilities the **concept of a 'sponsor'** of a clinical trial, in line with international guidelines, was introduced with Directive 2001/20/EC. This concept **should be upheld.**

(43) In practice, there may be loose, informal networks of researchers or research institutions which run jointly a clinical trial. **Those networks should be able to be co-sponsors of a clinical trial.** In order not to weaken the concept of responsibility in a clinical trial, where a clinical trial has several sponsors, they should all be subject to the obligations of a sponsor under this Regulation. **However, the co-sponsors should be able to split up the *responsibilities* of the sponsor by contractual agreement.**

What is a clinical trial?

‘Non-interventional study’: a clinical study other than a clinical trial;

(1) ‘Clinical study’: any investigation in relation to humans intended

(a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;

(b) to identify any adverse reactions to one or more medicinal products; or

(c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products;

with the objective of ascertaining their safety or efficacy.

(2) 'Clinical trial': a clinical study which fulfils any of the following conditions:

- **the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned;**
- **the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study;**
- **diagnostic or monitoring procedures in addition to normal clinical practice are applied**

Clinical Trial Regulation introduces Proportionate Regulation?

‘Low intervention trials’

The new Clinical Trial Regulation:

- Recognises they are of crucial importance to
  - assessment of standard treatments and diagnoses
  - optimising the use of medicinal products
  - contributing to a high level of public health.

- **Recogises they should be subject to less stringent rules**
- ***Proportionate***
  - ***Monitoring***
  - ***requirements for the contents of the master file***
  - ***traceability of investigational medicinal products***
  - ***shorter deadlines for approval***

What is a low intervention trial?

‘**Low-intervention clinical trial’:** a clinical trial which fulfils **all** of the following conditions:

(a) the investigational medicinal products***,*** *excluding placebos****,*** are authorised;

(b) according to the protocol of the clinical trial,

- the investigational medicinal products are used in accordance with the terms of the marketing authorisation or

- ***the*** use ***of the investigational medicinal products*** is ***evidence based and supported by published scientific evidence on safety and efficacy*** in any of the Member States concerned

(c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned

An interventional trial asks a question about a drug

Investigational
Medicinal
Product

The Clinical Trial Regulations apply to:

- **Protect the rights of the patient**
- **Ensure collection of full safety data on the IMP**
- **Ensure the integrity of the trial data**
- **Ensure insurance is provided to indemnify the risk of trial participation**

A low interventional trial asks a question about a drug

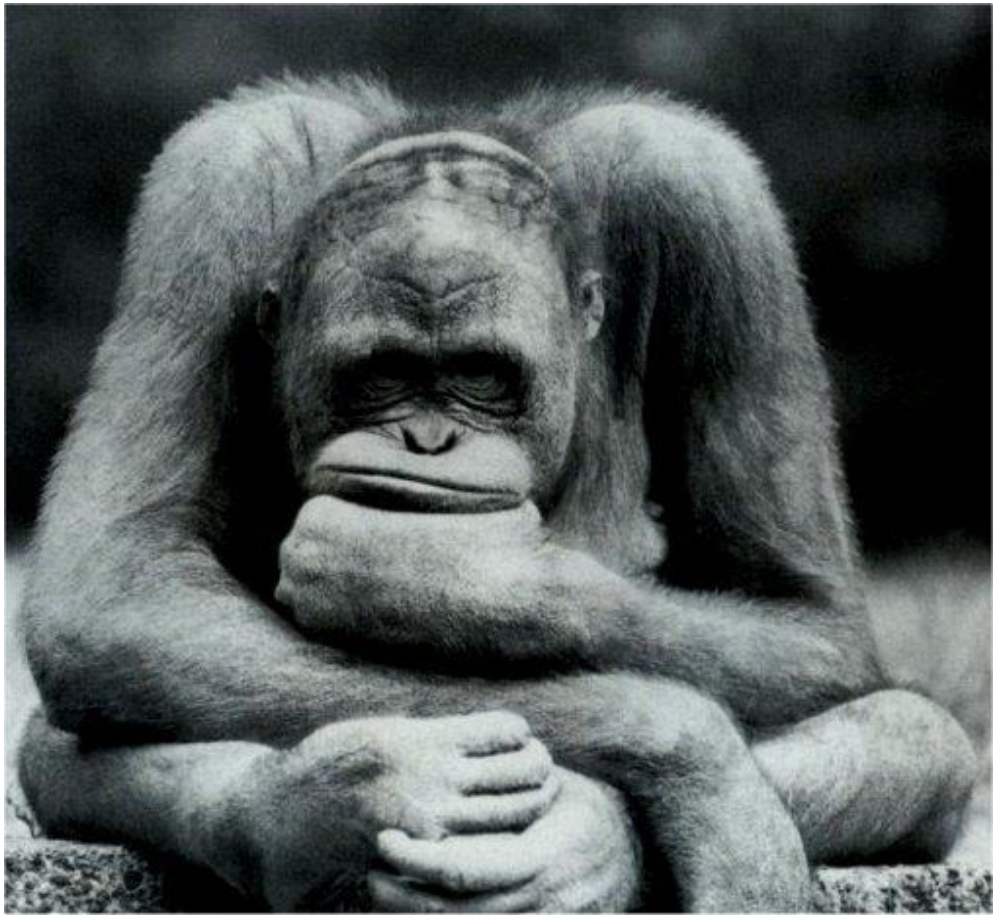
Investigational
Medicinal
Product

The Clinical Trial Regulations apply to:

- **Protect the rights of the patient**
- **Ensure collection of appropriate safety data on the IMP**
- **Ensure the integrity of the trial data**

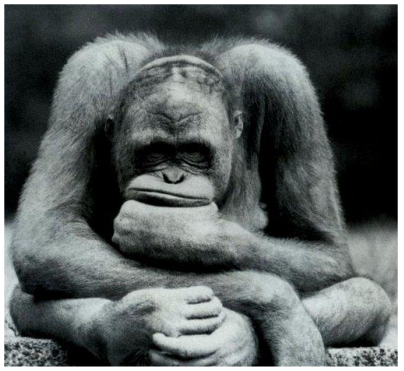
and additional insurance is not required as the risk of trial participation is not above standard clinical practice

Which Paediatric Oncology Trials can be defined as low intervention?



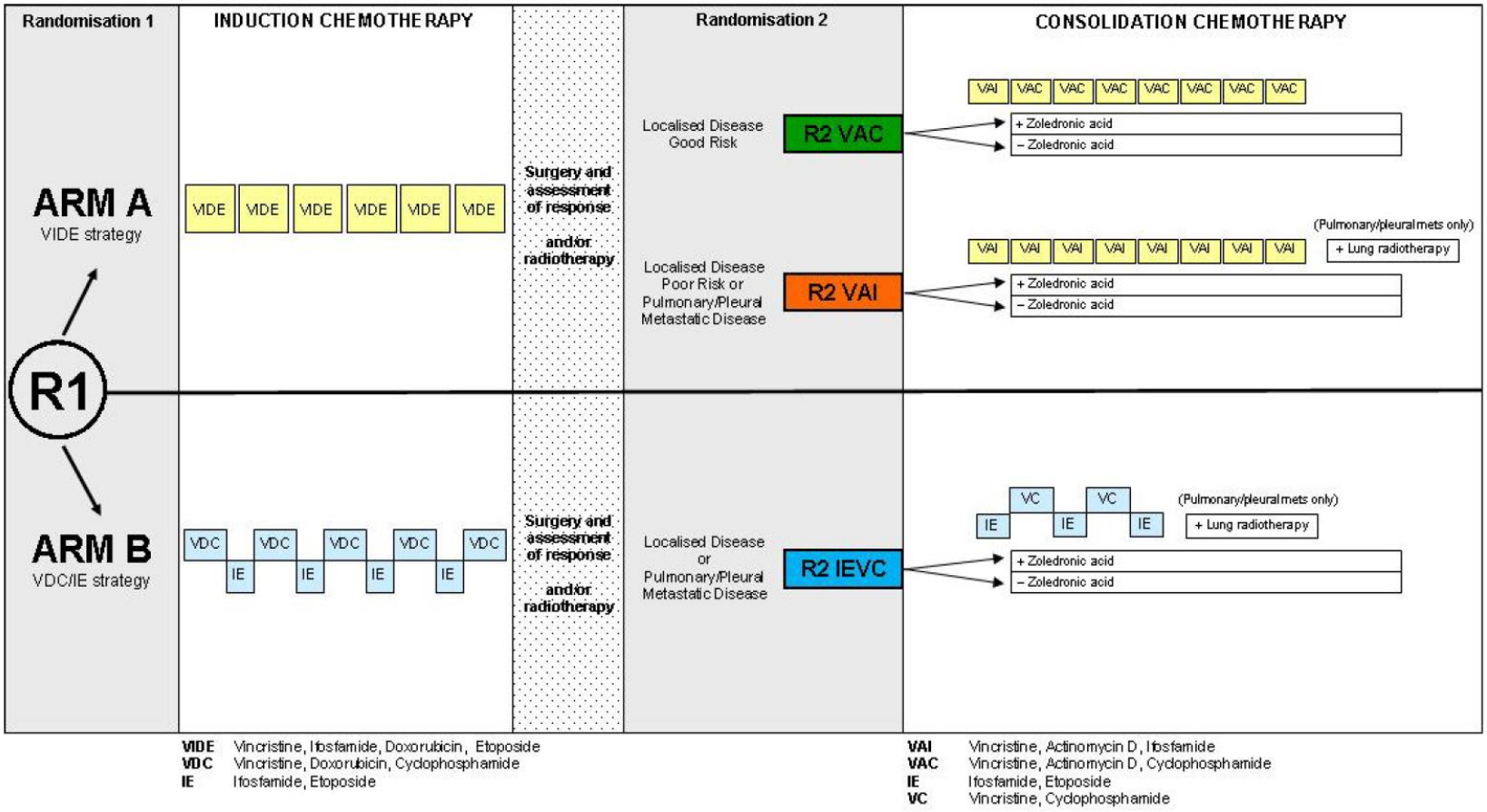
- Paediatric oncology clinical trial group trials MOSTLY use **only standard drugs**
  - Majority of trials aim to **improve the use of standard drugs**
  - **Majority of trials do not contribute to the label/license of a drug**

  - **MAJORITY OF TRIALS SHOULD BE CATEGORSIED AS LOW INTERVENTION TRIALS ?**



Euro-Ewings 2012 Trial

TRIAL SCHEMA



Euro-Ewings 2012 Trial

EU standard Treatment

Vincristine
Ifosfamide
Doxorubicin
Etoposide

X

6 courses

vs

US standard Treatment

Vincristine
Doxorubicin
Cyclophosphamide
Ifosfamide
Etoposide

X

5 courses

(a) the IMPs**,** are authorised;

(b) according to the protocol of the clinical trial,

- the IMPs are used in accordance with the terms of the marketing authorisation or
- ***the*** use ***of the IMPS*** is ***evidence based and supported by published scientific evidence on safety and efficacy*** in any of the Member States concerned

(c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned

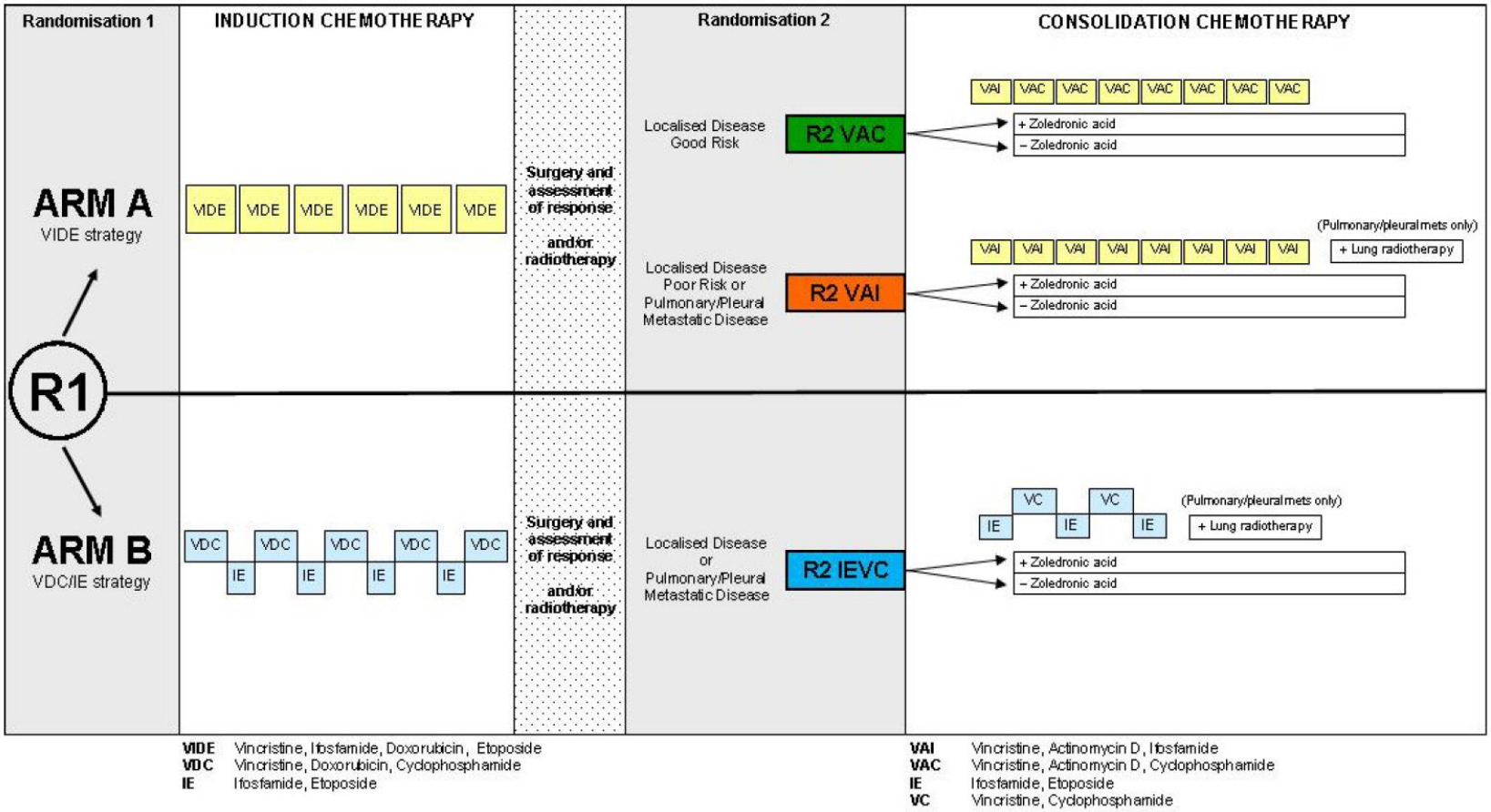
5 IMPs: all with marketing authorisation

If ‘Low Interventional Trial’ Category applies

- **Under the CTR :**
  - Short timeline for clinical trial authorisation
  - **No change in definition of IMPs** but
    - Risk adjusted monitoring
    - Reduced labeling requirement for IMPs
    - Proportionate drug accountability
    - Proportionate safety reporting
  - Modified insurance requirement

Euro-Ewings 2012 Trial

TRIAL SCHEMA



Can SIOP-E smooth the way?

SIOP-E Platform to facilitate the implementation of European Clinical Trials Groups research strategy:

- **the Clinical Trial Facilitation Platform**

SIOP-E Clinical Trials Facilitation Platform

THE NEED

Optimisation of the Framework in which we deliver collaborative academic sponsored clinical trials

- **Addresses the key Challenges:**
  - **Inter-country differences**
    - **Healthcare and research frameworks**
      - **Regulatory complexity**
        - **Contractual negotiations**
          - **Funding /resources**

It all takes too long ☹

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SIOP-E Clinical Trials Facilitation Platform

- Some work already achieved
  - SIOP-E Clinical Contract template
  - SIOP-E Protocol template

encca
European Network for Cancer research in Children and Adolescents

- Role of a Trial Sponsor in the EU
  - ITCC Sponsors Committee and Consortium

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SPONSOR INSTITUTIONS COMMITTEE

Aims

- A **consortium of ITCC European Sponsoring Institutions** and **National Coordinating Centres**
  - Selection based on an **independent review** of their expertise and infrastructure
- Improve our understanding of the infrastructure and processes of members of the Consortium
- **Share experience and best practice** between the member institutions
- **Develop harmonised approaches to European sponsorship**

Outputs to date

- Clinical Study Co-ordination Agreement
  - Sponsor -> National Co-ordinating Centres responsibilities
- Clinical Trial Insurance Database of national requirements
- Trial protocols
  - Draft guidance on national regulatory requirements
- Funding models
  - Glossary of national & international funding sources
  - Glossary of costings for ITCC trials
    - work in progress
- Pharmacovigilance guidelines
  - National PV guidelines including for US
- Risk assessment and monitoring plan guidelines for ITCC trials
  - Work in progress

Establishing the SIOP-E Clinical Trials Facilitation Platform

- Assess and meet the needs of the SIOP-E clinical trials community
  - Work together to deliver support and guidance to accelerate trial delivery
    - Implementation of the CTR (2017/18)
    - Agreement on interpretation of definitions within the CTR
  - Optimise quality of collaborative clinical trials
  - Horizon scan for funding opportunities
  - Horizon scan for potential Policy changes that impact on clinical trials

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Clinical Trial Facilitation Platform

Milestones	Target Date
Assess the needs of the SIOP-E clinical trials community (questionnaire)	April 2016
Map The framework of the Toolkit (including prioritisation of development of guidance documents and templates)	June 2016
Review implementation process of Clinical Trial Regulation	Mid 2017
Delivery of key Clinical Trials guidance documents: Defining low intervention for paediatric oncology trials	End of 2017
Create a SIOP-E Clinical Trials Advisory Office	~

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Final Thoughts

- Paediatric Oncology has been at the forefront of trials research for decades
  - Lets stay there !
  - Lets work together to
    - overcome the regulatory challenges
    - accelerate delivery of academic led trials
    - continue to deliver well designed clinical trials
    - Continue to improve treatments for all children and adolescents diagnosed with cancer

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Paediatric Oncology Clinical Trials in Europe

Strengthened by networks

Adapting to the Regulations

Thank you for listening

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