

# The EU Clinical Trial Directive and Pharmacovigilance Obligations

- a UK perspective

***Dr Philip Harrison***

*BSc MB ChB MRCP FFPM*

**Senior Medical Assessor**

***Clinical Trials Unit***

# Clinical Trials Directive – 2001/20/EC

*“Directive relating to the **implementation of good clinical practice** in the conduct of clinical trials on medicinal products for human use in EU”*

*“.....necessary to **simplify and harmonise** the administrative provisions governing such trials ...” [in the EU]*

***All Clinical Trials** including PAS but not non-interventional trials*

Articles 1.1 & 1.4

# PHARMACOVIGILANCE

GENERAL PROVISIONS

GMP: MANUFACTURE AND IMPORT OF IMPs

SCOPE

LABELLING

DEFINITIONS

**SINGLE APPROVAL SYSTEM IN UK FOR CLINICAL TRIALS SI 1031 & the EU**

PROTECTION OF CLINICAL TRIAL SUBJECTS

**INSPECTION** - VERIFICATION OF GCP, PhV & GMP

CLINICAL TRIALS ON MINORS

COMMENCEMENT OF A CLINICAL TRIAL

CLINICAL TRIALS ON INCAPACITATED ADULTS NOT ABLE TO GIVE INFORMED CONSENT

CONDUCT OF CLINICAL TRIALS

ETHICS COMMITTEES

SINGLE PROCESS, EOS, SUSPENSION/AMENDMENT OF A TRIAL

SINGLE OPINION per MS

**EXCHANGE OF INFORMATION**

---

STATUTORY INSTRUMENTS

---

**2004 No. 1031**

**MEDICINES**

The Medicines for Human Use (Clinical Trials) Regulations  
2004

<i>Made</i>	- - - -	<i>31<sup>st</sup> March 2004</i>
<i>Laid before Parliament</i>		<i>1<sup>st</sup> April 2004</i>
<i>Coming into force</i>	- -	<i>1st May 2004</i>

# Europe and the CTD?

- ▶ Effective 1<sup>st</sup> May 2004
  - ▶▶ UK, Ireland, Belgium, Spain, Austria, Sweden, Denmark and Accession Member States (except Poland & Lithuania)
- ▶ Pending
  - ▶▶ Finland, Greece, Italy & Poland
- ▶ Implementation delayed
  - ▶▶ France (Q4/Q1), Germany (Q3/Q4), Netherlands (Q3), Luxembourg, Portugal and Lithuania

# New Challenges for Industry

- ▶ **New Pharmacovigilance requirements**
  - ▶ SUSARs
  - ▶ Independent Safety Monitoring Committees (DSMBs etc)
  - ▶ Annual Safety Reporting
- ▶ **New EU databases/e-reporting**
  - ▶ EudraCT
  - ▶ EudraVigilance CT Module (EV CTM)
  - ▶ Ongoing DB development – EMEA TIG, JIGs, Task Forces.
- ▶ **New accountabilities**
  - ▶ GCP & PhV inspection
- ▶ **New Quasi-Authorities**
  - ▶ EU CT Facilitation Group (CTFG) + PhV WP

# Key Reference Documents

<http://www.emea.eu.int/index/indexh1.htm>

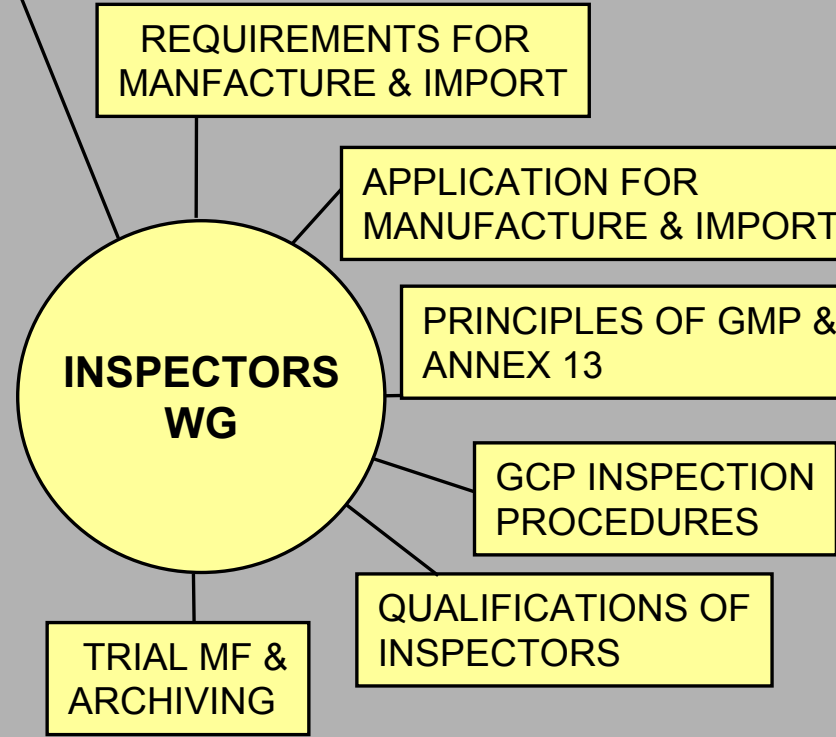
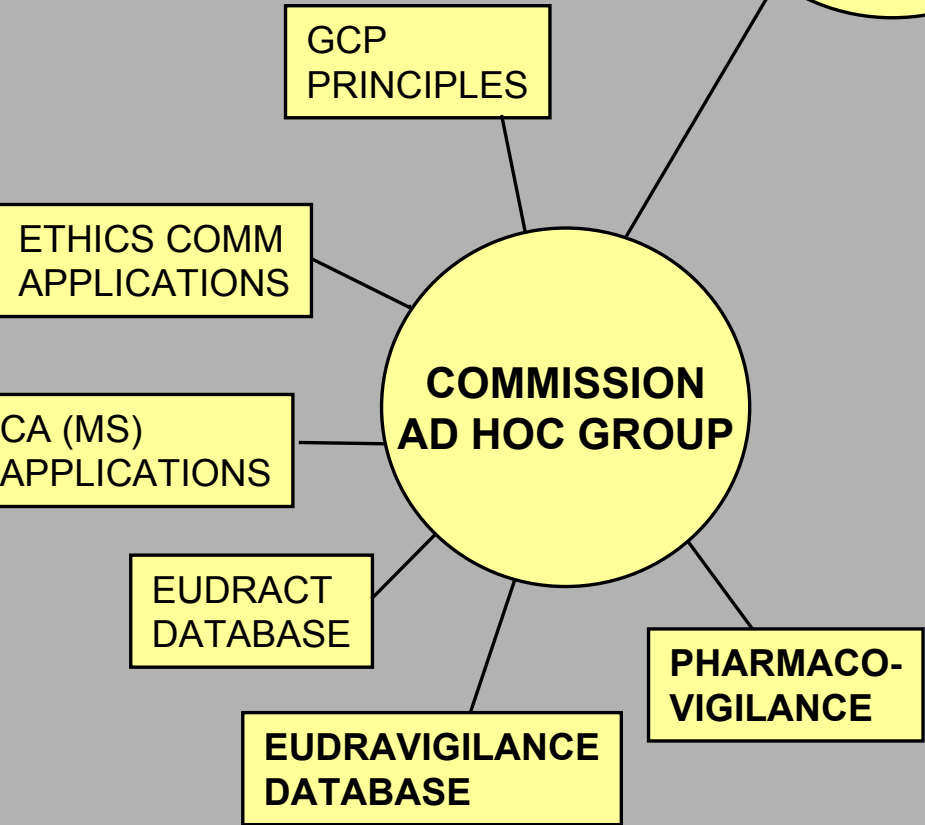
- ▶ A very large amount of guidance relating to the development of medicines (EMA, FDA)
  - ▶▶ Specific Issues
    - » Methodologies utilised – GCP, CTs, Stats, special populations
    - » Current requirements for development – specific diseases or disease territories – COPD and Oncology
  - ▶▶ Protecting patients
    - » Informed consent, DH, pharmacovigilance
    - » Paper trail, audit, inspection
  - ▶▶ Protecting data integrity
    - » Monitoring, audit, inspection
    - » Automated collection/validation

NB. Statistical surveillance – not yet addressed by RAs.

**Commission Directives**  
**GMP DIRECTIVE** (2003/94/EC)  
**GCP DIRECTIVE** (pending)

**Council Directive**  
**2001/20/EC**  
**ELEVEN GUIDANCE DOCUMENTS**

**EC COMMISSION GUIDELINES**



# Clinical Trials Directive (2001/20/EC)

## Pharmacovigilance-related articles

EU CT Directive Articles 16 & 17.

UK SI 1031 Part 5 Regulations 32 – 35

- ▶ **Definitions** (Dir. Article 2, ENTR/CT3 + Annex 1, SI Part 1 Reg 2.1)
- ▶ **Collection and notification of adverse events** (CTD Article 16, ENTR/CT3 & SI Part 5 Reg 32)
- ▶ **Notification of serious adverse reactions**  
(Article 17, ENTR/CT3 & SI Part 5 Reg 33 )
- ▶ **Guidance** (Directive Article 18/ENTR/CT 3 & 4, pending in UK)

# EU COMMISSION GUIDANCE DOCUMENTS

▶ **Pharmacovigilance Guideline** ENTR/CT3 Article 18

*“Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use”*

▶ **EudraVigilance Guideline - Clinical Trial Module** ENTR/CT4  
(EV CTM) Article (11 &) 17

*“Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (SUSARs)”*

*<http://www.mhra.gov.uk>, <http://eudract.emea.eu.int/> and <http://pharmacos.eudra.org/F2/pharmacos/new.htm>*

# Key Reference Documents

A lot of guidance on managing safety Information

## ▶ Regional regulatory guidelines

### ▶▶ **CT DIRECTIVE** (EU Commission Web Site + *Official Journal*)

- » CTA (ENTR/CT1\*), GMP, (EMEA) GCP (ICH E6 - CPMP/ICH135/95), EC (ENTR/CT2\*)
- » Pharmacovigilance
  - SUSAR/PhV (ENTR/CT3\*)
  - EV DATABASE (ENTR/CT4\*) + 9 others

### ▶▶ **MHRA WEB SITE** guidance with links to EudraCT and EudraVigilance

### ▶▶ **FDA WEB SITE**

- » US IND \* **EMEA/EudraCT** or via **MHRA Web site**
- » Safety Monitoring Boards – DSMBs etc. (Nov 2001)
- » FITM Draft guidance for industry and reviewers: *Estimating the safe starting dose in clinical trials for therapeutics in adult healthy volunteers.* (December 2002)
- » Consultation paper: “The TOME” Safety reporting requirements for Human drug and biological products (14<sup>th</sup> March 2003)
- » Concept papers (3<sup>rd</sup> March 2003) ‘*Pre-marketing risk Assessment*’, ‘*Risk assessment of observational trials*’ & ‘*Risk management programs*’

# INVESTIGATOR: Notification of Adverse Events (Article 16, SI Part 5 Art 32)

- ▶ ***The investigator to report all SAEs “immediately” to the sponsor***
  - ▶ usually means within 24 – 48 hours
  - ▶ except for those exempted by the protocol or the IB (not the norm)
  - ▶ each immediate report to be followed by a detailed written report (narrative)
  - ▶ each report should identify the subject by a unique code number
- ▶ ***The investigator should provide the sponsor with any additional information requested for reported deaths***
- ▶ ***Adverse events and/or laboratory abnormalities identified in the protocol*** as critical to the safety evaluation to be reported to the sponsor in accordance with reporting requirements and time periods specified within the protocol (may be specified in protocol or subsequently by CAs, RECs, SMCs).
- ▶ ***The sponsor should keep detailed records*** of all adverse events reported to him; these should be submitted to the Member State(s) where the clinical trial is being conducted, upon request.

# Communications to investigators

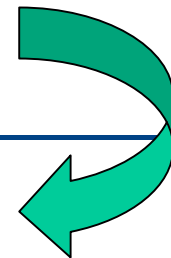
- ▶ **Significant safety issues** should be notified as soon as possible to all investigators
- ▶ **Safety issue that impacts upon the course of the clinical study** or development project should be considered significant; includes
  - ▶▶ suspension of the study programme
  - ▶▶ safety-related amendments to study protocols

# E2A DEFINITIONS confirmed + SUSARs

CPMP/ICH/377/95 , CTD Art 17, SI Part 5, Art 33

- ▶ Adverse event (non-serious = AE)
- ▶ Adverse reaction (non-serious = ADR)
- ▶ Expedited reporting (SAEs 24-48 hrs; SUSARS 7/15 days)
- ▶ Serious adverse event (SAE)
- ▶ Serious adverse reaction (SADR NB. suspected ADR in US)
- ▶ Serious expected adverse reaction
- ▶ Serious unexpected adverse reaction (SUAR)

- 
- ▶ **SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR)**



# SUSAR - OLD CONCEPT, NEW TERMINOLOGY

## DEFINITIONS as per E2A (CPMP/ICH/377/95)

### ▶ **Suspected Unexpected Serious Adverse (drug) reaction (UK SUAR = SUSAR)**

▶▶ *A reported serious adverse event considered either in the investigator or sponsors opinion to be possibly or probably related to the test medication and for which the nature and/or severity is not consistent with the current product information (For an unapproved investigational medicinal product [an IMP] listed in the Investigator's Brochure.)*

### ▶ **Serious – Unexpected - Related**

Reasonable suspected causal relationship NOT “cannot be ruled out”. Cannot be downgraded by Sponsor but can be upgraded.

### ▶ **Unblinded for reporting to UK CA/REC & EV CTM**

# SUSAR expedited reporting

.....associated with:

- ▶ the IMP(s) and which occur in the **concerned trial**  
Includes all experimental and licensed comparators.
- ▶ the IMP being tested in a clinical trial **in the EU** and which occur in a trial conducted by the **same sponsor in a third country** (i.e. in non EU countries)
- ▶ **spontaneous reports** or those from within publication (EV CTD unless EU MA)
- ▶ reports transmitted to the sponsor by **another regulatory authority** (ad hoc analyses, concerns)

# Expedited Reporting requirements – E2A

CPMP/ICH/377/95 + ENTR/CT3 + SI Part 5 Art 33.

- ▶ **7-day initial reports:** fatal/life-threatening unexpected ADRs
  - ▶▶ Identifying follow-up information 15 days and developments ASAP
- ▶ **15-day reports:** other serious unexpected ADRs
- ▶ **Identifiable source, product, subject, (serious, unexpected, possible causality), trial and individual identifiers.**
- 1. All SUSARs WW to Competent Authorities (CA/CMS – Annex 2 ENTR/CT3)**
- 2. Option to restrict SUSAR reporting within cMS:**
  - i. Concerned (relevant) Research Ethics Committees (UNBLINDING) - COREC
  - ii. Principal Investigator(s) in MS

*Providing that other EU third country data are reported periodically and any increasing safety hazard notified as appropriate. BLINDS MAY REMAIN IN PLACE FOR INVESTIGATORS (logistics).*
  - iii. Competent Authorities after EV CTM (NB. not addressed by EC at present) however, *UNBLINDING REQUIRED now and in future.*

# Other requirements for expedited reports

- ▶ **All case reports on novel or comparator IMP will require:**
  - ▶▶ **Causality (relatedness) assessments** (*investigator +/- sponsor*)
    - » will apply usually to serious and non-serious adverts
    - » submitted reports should include both the investigator and sponsor causality assessments, if there is not agreement on causality
  - ▶▶ **Assessment of expectedness** (*sponsor*)
    - » *Investigators Brochure (novel product)*
    - » *SPC (marketed product)*
    - » *SMC Charter (blinded study with known high morbidity/mortality)*
  - ▶▶ **Treatment codes broken prior to submission of SUSARs** (*independent party not involved in study – PhV? CRO? SMC?*)
    - » 'blind' to be maintained for persons responsible for the analysis and interpretation of results
    - » "waivers" (stated endpoints, expected morbidity) granted in agreement with competent authorities NOTE: these are **NOT** SUSARS. Usually an SMC in place.
  
- ▶ **Placebo cases NOT subject to expedited reporting, unless suspected reaction due to excipient.**

# Other requirements for expedited reporting – to CA/REC and Investigator

- ▶ **Events which materially alter the benefit-risk ratio** (Safety alerts based upon aggregated analyses, SMC recommendations etc. includes SARS but also other hazards – disease or demography-related issues, comeds, drug interactions, invasive trial procedures).
  
- ▶ **Events which impact on trial conduct or drug administration:**
  - ▶▶ Serious expected ADR with *unexpected outcome* e.g. death
  - ▶▶ *Increase frequency of serious expected* ADR (if important)
  - ▶▶ *Post-study* SUSARs (after trial completion – WD effects, exacerbation of illness due to loss of efficacy)
  - ▶▶ New event relating to trial conduct likely to affect subject safety
    - ▶▶ *SAE* assoc with trial procedure which could **impact on conduct**
    - ▶▶ *Significant hazard* to trial population e.g lack of efficacy
    - ▶▶ *Non-human studies:* Major safety finding from newly completed non-clinical study (tox, repro, carc studies)

NOTE: Trials requiring **early termination** – end of study (EOS) notification in **15 days** – but safety-related issues may require expedited reporting rather than awaiting ASR (7/15 days).

# Format of SUSAR reports - E2BM

CPMP/ICH/287/95

- ▶ **Data elements specified in Annex 3 of guideline ENTR/CT3**
  - ▶▶ reports to include 'Eudract' number plus sponsor's case report reference number
  - ▶▶ reports with insufficient information may be returned to the company for completion and re-submission
- ▶ **Electronic reporting - *expected method* for expedited reporting of SUSARs to the CA**
  - ▶▶ format and content as defined within E2B (M)
  - ▶▶ Awaiting Commission guidance on mandatory status
- ▶ **CIOMS-I form accepted (for now).**
  - ▶▶ when available, basic information/data elements, as described in Annex 3, be included in any report (not as detailed as E2B)
- ▶ **Other important observations** qualifying for expedited reporting should be notified by letter; should reference Eudract number(s) and title(s) of trial(s) concerned

# Annual Safety Reports

CTD Article 17.2 ENR/CT3 & SI Part 5, Article 35

- ▶ The sponsor must provide annually a **benefit-risk assessment** and a concise **safety overview** for the clinical trial and/or for all concerned clinical trials conducted **world wide** on the tested investigational medicine
  - ▶▶ should be related to the overall safety of the IMP being tested
  - ▶▶ should be complemented with an analysis of the implications for the population of the clinical trial themselves

# Annual Safety Reports

## TO WHOM?

### Sponsor must provide report annually to:

1. **Competent Authority** (MHRA in the UK)
2. **Research Ethics Committee** (authorised by UKECA and relevant to trial)

Not obliged to send to investigators (nor precluded from providing) – although change in B:R or emerging safety issues must be communicated to them at any time. This may be in the form of an updated IB/SPC.

## CONTENT OF REPORT?

- ▶ Report must address expected serious as well as unexpected – CT SARS & spontaneous from other MS or third countries

They are NOT ASURs in concept or format. May be annexed to PSUR for EU marketed product.

1. **Report on 'subject safety' (safety overview)** – Executive Summary, narrative on B:R and emerging safety issues *or no change/lack of them*.
2. **Aggregated tabulations (by study)**
3. **SAE line listings (by study) – unexpected identified**
4. **Other? Product and issue specific.**

# Annual Safety Reports

- ▶ **Following points to be considered:**
  - ▶ relation with **dose, duration, time course** of the treatment
  - ▶ **reversibility**
  - ▶ evidence of **previously unidentified toxicity** in the trial subjects
  - ▶ **increased frequency** of toxicity
  - ▶ **interactions** or other associated **risks factors**
  - ▶ any specific safety issues related to **special populations** such as the elderly, the children or any other at risk groups
  - ▶ positive and negative experiences during **pregnancy or lactation**
  - ▶ **abuse, overdose** and its treatment
  - ▶ **risks** which might be associated with the **investigation or diagnostic procedures** of the clinical trial

# Aggregate Summary Tabulations

- ▶ **Summary tabulations of serious ADR terms across all patients to be presented**
  - ▶▶ will usually contain more terms than subjects
  - ▶▶ when the number of cases is very small, narrative description may be more suitable
- ▶ **Aggregate summary tabulation should specify the number of reports**
  - ▶▶ for each body system
  - ▶▶ for each ADR term
  - ▶▶ for each treatment arm, if applicable
- ▶ **Unexpected ADR terms should be clearly identified in the tabulation**
- ▶ **Sample table provided in Annex 5 of Guideline ENTR/CT3**

# Annual Safety Reports

- ▶ Consider supporting **results of non-clinical studies** or other experience with the IMP are likely to affect the subjects' safety.
- ▶ **Measures proposed to minimise risks** identified should be detailed (previously or currently).
- ▶ Rationale for **amendments of IB, protocol, PIL or consent form**

# Line Listings

- ▶ **Examples presented in Annex 4 of Guideline ENTR/CT3**
- ▶ **Should include each subject only once**
- ▶ **If more than one ADR, they should all be mentioned but listed under the most serious ADR, as judged by the sponsor**
- ▶ **If the same subject experiences different ADRs on different occasions, these should be treated as separate reports**
  - ▶ the same subject might then be included in a line listing more than once
  - ▶ the line listings should be cross-referenced when possible
- ▶ **Cases should be tabulated by body system (SOC - standard system organ classification scheme in MedDRA)**
- ▶ **One listing for each trial** - additional listings may be provided when appropriate and relevant

# Time frame for ASR

- ▶ **Starts with *date of first authorisation of clinical trial*** by CA in any Member State
  - ▶▶ Future data lock points should be based upon this date (negotiation possible). PSURs?
  - ▶▶ [*Summary!!*] reports to be submitted within **60 days** of the data lock point (1-3 pages?)
- ▶ **Short term trials** (i.e. finished within 6 months): report to be notified within 90 days of the end-of-trial
- ▶ **Reporting period ends** after close of the final clinical trial/s in last Member State

NOTE: Trials requiring **early termination** – end of study (EOS) notification in **15 days** – but safety-related issues may require expedited reporting rather than awaiting ASR (7/15 days).

# Investigators: Line listings

- ▶ **Sponsor should inform all concerned investigators** with regards to findings that could adversely affect the safety of study subjects

## **NOTE: With agreement of concerned REC:**

- ▶ Information can be aggregated in a **line listing of WW SUSARs**
  - ▶▶ Periodicity to be determined by nature of the clinical development project and the volume of SUSARs generated
  - ▶▶ should be accompanied by concise summary of the evolving safety profile of the investigational product
- ▶ **Blinded trials:** SUSARs remain blinded to investigator/REC.

# EudraVigilance - Clinical Trial Module

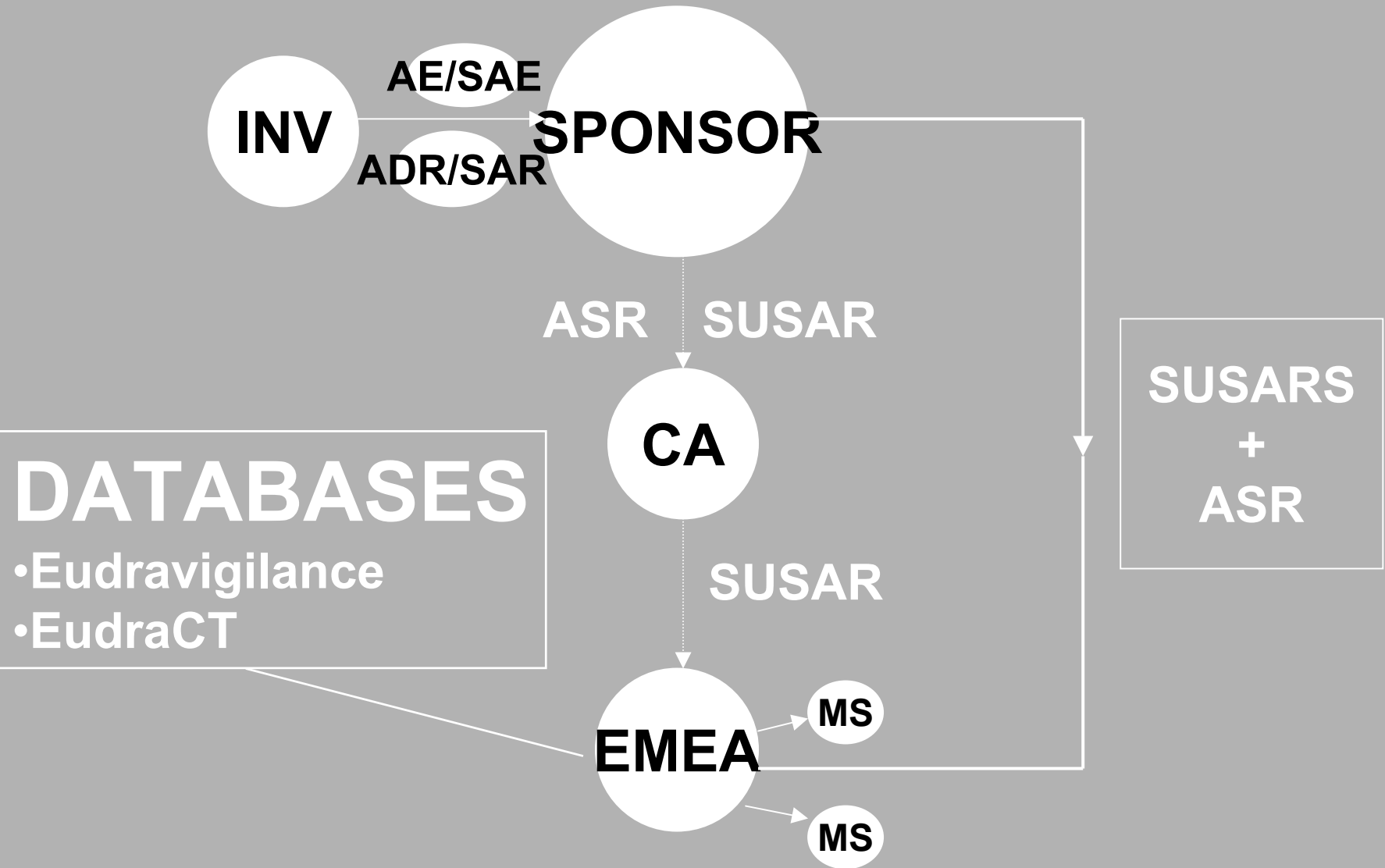
ENTR/CT4

- ▶ Now established and will be fully maintained by the EMEA for access by EU CAs, EMEA and EU Commission.
  - Will create a single overall database for 25 European regulatory authorities covering clinical trial and post-marketing safety reporting
  - Cyclone E2B gateway/Web Trader – identical look and feel (+ automated data entry)
  - Functionality – signal detection and aggregated analyses – under construction
  - Eventually to be closely linked to the ‘Eudract’ database (register of all clinical trials conducted in the EU) – not yet initiated until post Phase II EudraCT
  
- ▶ Access to database restricted to 25 EU Competent Authorities, the EMEA and the European Commission
  - Role of MS/CA/EMEA in recording/cleaning data
  - Reports from third countries – direct entry
  - Duplicate reports – automated data cleaning

# EudraVigilance - Clinical Trial Module

ENTR/CT4

- ▶ **Member States to be responsible *for ensuring* that the sponsor reports all SUSARS electronically to the database**
  - ▶▶ each trial to be identified by a 'Eudract' clinical trial number
  - ▶▶ sponsor protocol code to be entered on all reports: will serve to identify studies conducted entirely outside the EU
  
- ▶ **Confidentiality – patients/sponsor**
  - ▶▶ identity in report forms should be codified
  - ▶▶ only authorised persons access to identifiable 'personal' details, to permit data verification procedures, review or inspection of such data



# CHANGES IN UK CT SYSTEM (1)

- 1. CTA** - *New Regulatory Approach (CA, CTA, no exemptions - DDX, CTX, CTMP & CTCs, protocol and IMPD amendments, EOS declarations)*
- 2. Legal underpinning** of ICH GCP & GMP (*GMP/GCP Directives & Guidance*)
- 3. Statutory basis for Ethics Committees (UKECA)**

<http://www.corec.org.uk/form.htm>

- 4. Phase I & ALL Phase IV studies** (*+ PA commitments*) included in definition of CT. *“Interventional” but nor “mechanistic studies.*
- 5. Verification** – *GMP & GCP Inspection – Manufacturer, CROs, SMOs, Sponsor/MAH, investigator.*

# CHANGES IN UK CT SYSTEM (2)

6. **IMPD:** *Summarised pharmaceutical, non-clinical and clinical assessments required in all MS (CAs) – no change for UK.*
7. **Pharmacovigilance**
  - ▶▶ *Expedited safety reports (SUSARs) – no change for UK*
  - ▶▶ *ASR reports by sponsor to CA/ERCs*
8. **Exchange information on clinical trials and ADR reports with CA, EU Com and EMEA**
  - ▶▶ *Co-ordination of regulatory decisions in EU*
  - ▶▶ *EU Databases*
9. **Fees**

# The UK Competent Authority

# Thank You

Philip Harrison