Master di Secondo Livello in "Aspetti Regolatori, Brevettuali ed Economici dello Sviluppo dei Farmaci e dei Dispositivi Medici"

# "L'Organizzazione e le Attività dell'AIFA nell'ambito della Sperimentazione Clinica, il Nuovo Regolamento Europeo, il Portale Europeo e le Procedure VHP"

Diego Alejandro Dri

Roma, 22 settembre 2017

# Dichiarazione di trasparenza/interessi*

Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo l'AIFA

| Interessi nell'industria farmaceutica | NO | Attualmente | Da 0 a 3 anni precedenti | oltre 3 anni precedenti |
|---|---|---|---|---|
| *INTERESSI DIRETTI:* | | | | |
| 1.1 Impiego per una società: Ruolo esecutivo in una società farmaceutica | ☒ | ☐ | ☐ | ☐ obbligatorio |
| 1.2 Impiego per una società: Ruolo guida nello sviluppo di un prodotto farmaceutico | ☒ | ☐ | ☐ | ☐ obbligatorio |
| 1.3 Impiego per una società: altre attività | ☐ | ☐ | ☒ | ☐ facoltativo |
| 2. Consulenza per una società | ☒ | ☐ | ☐ | ☐ facoltativo |
| 3. Consulente strategico per una società | ☒ | ☐ | ☐ | ☐ facoltativo |
| 4. Interessi finanziari | ☐ | ☐ | ☒ | ☐ facoltativo |
| 5. Titolarità di un brevetto | ☒ | ☐ | ☐ | ☐ facoltativo |
| *INTERESSI INDIRETTI:* | | | | |
| 6. Sperimentatore principale | ☒ | ☐ | ☐ | ☐ facoltativo |
| 7. Sperimentatore | ☒ | ☐ | ☐ | ☐ facoltativo |
| 8. Sovvenzioni o altri fondi finanziari | ☒ | ☐ | ☐ | ☐ facoltativo |
| 9. Interessi Familiari | ☐ | ☒ | ☐ | ☐ facoltativo |

* Diego Alejandro Dri, secondo il regolamento sul Conflitto di Interessi approvato dal CdA AIFA in data 25.03.2015 e pubblicato sulla Gazzetta Ufficiale del 15.05.2015 in accordo con la policy EMA /626261/2014 sulla gestione del conflitto di interessi dei membri dei Comitati Scientifici e degli esperti.

N.B. Il compenso ricevuto per questo intervento è regolato dalla contrattazione collettiva.

# Agenda

- L'Organizzazione e le Attività dell'AIFA nell'ambito della Sperimentazione Clinica
- Il nuovo Regolamento Europeo
- Il Portale Europeo
- Procedure VHP

# L'Organizzazione e le Attività dell'AIFA nell'ambito della Sperimentazione Clinica

Agenzia Italiana del Farmaco
AIFA

# L'Agenzia Italiana del Farmaco

- L'Agenzia Italiana del Farmaco è l'autorità nazionale competente per l'attività regolatoria dei farmaci in Italia.

- E' un Ente pubblico che opera in autonomia, trasparenza e economicità, sotto la direzione del Ministero della Salute e la vigilanza del Ministero della Salute e del Ministero dell'Economia.

- Collabora con le Regioni, l'Istituto Superiore di Sanità, gli Istituti di Ricovero e Cura a Carattere Scientifico, le Associazioni dei pazienti, i Medici e le Società Scientifiche, il mondo produttivo e distributivo.

# Funzioni (1/2)

- garantisce l'accesso al farmaco e il suo impiego sicuro ed appropriato come strumento di difesa della salute
- assicura la unitarietà nazionale del sistema farmaceutico d'intesa con le Regioni
- provvede al governo della spesa farmaceutica in un contesto di compatibilità economico-finanziaria e competitività dell'industria farmaceutica
- assicura innovazione, efficienza e semplificazione delle procedure registrative, in particolare per determinare un accesso rapido ai farmaci innovativi ed ai farmaci per le malattie rare

# Funzioni (2/2)

- rafforza i rapporti con le Agenzie degli altri Paesi, con l'Agenzia Europea dei Medicinali (EMA) e con gli altri organismi internazionali

- favorisce e premia gli investimenti in Ricerca e Sviluppo (R&S) in Italia, promuovendo e premiando la innovatività

- dialoga ed interagisce con la comunità delle associazioni dei malati e con il mondo medico-scientifico e delle imprese produttive e distributive

- promuove la conoscenza e la cultura sul farmaco e la raccolta e valutazione delle best practices internazionali.

# Mission

- Contribuire alla tutela della salute attraverso i farmaci
- Studiare e promuovere strumenti per favorire l'equilibrio economico di sistema attraverso il rispetto dei tetti di spesa farmaceutica programmati
- Garantire l'unitarietà sul territorio del sistema farmaceutico
- Promuovere la ricerca indipendente sui farmaci e gli investimenti R&S nel settore farmaceutico in Italia
- Rafforzare l'autorevolezza dell'AIFA in ambito nazionale ed internazionale
- Sviluppare ed implementare l'autonomia organizzativa-gestionale

# Commissioni consultive e tecnico scientifiche

AIFA è supportata dalla attività di due Commissioni tecnico-scientifiche composte da esperti di comprovata e documentata esperienza nel settore.

## Commissione Tecnico Scientifica (CTS)

attività connesse alle domande di Autorizzazione in Commercio di nuovi medicinali - sia per procedura nazionale, sia comunitaria - dei quali determina il rapporto costo-efficacia. Valuta ed esprime parere consultivo sulla classificazione dei farmaci ai fini della rimborsabilità.

## Comitato Prezzi e Rimborso (CPR)

svolge l'attività negoziale connessa alla rimborsabilità dei farmaci e le determinazioni vengono poi sottoposte alla valutazione della CTS per il parere definitivo.

# Osservatori

Gli Osservatori e le banche-dati sono gli strumenti essenziali con i quali l'AIFA controlla ed analizza il consumo dei farmaci a livello nazionale, regionale e locale, opera il monitoraggio delle sperimentazioni cliniche approvate dai Comitati etici locali ed integra le informazioni derivanti dalla rete nazionale di Farmacovigilanza.

Rete nazionale di farmacovigilanza

Attraverso la rete nazionale di farmacovigilanza raccoglie tutte le segnalazioni delle reazioni avverse e sorveglia sul profilo di beneficio-rischio dei farmaci; si integra con la Banca dati europea EUDRA Vigilance, pubblica il rapporto annuale sulla Farmacovigilanza in Italia.

# Osservatori

Osservatorio nazionale sull'impiego dei medicinali (OsMED)

Attua il monitoraggio di tutti i farmaci prescritti a carico del SSN e trasmette mensilmente dati alle Regioni secondo indicatori predefiniti di consumo e di spesa; pubblica il rapporto annuale sull'impiego dei medicinali in Italia.

Osservatorio Nazionale sulla Sperimentazione Clinica (OsSC)

Assicura il monitoraggio di tutte le sperimentazioni cliniche condotte in Italia e approvate dai Comitati Etici locali; pubblica il rapporto annuale sulla Sperimentazione Clinica in Italia.

# Segretariati e Comitati Consultivi

- L'Agenzia Italiana del Farmaco ha nominato i suoi nuovi organismi consultivi che andranno a potenziare l'attività di valutazione scientifica e regolatoria dell'Agenzia, avvalendosi del contributo di alcuni tra i massimi esperti in Italia delle principali aree terapeutiche per cui sono in corso di registrazione i nuovi farmaci.

- Gli organismi di nuova istituzione qualora richiesti forniranno un contributo prezioso all'attività della Commissione Tecnico Scientifica (CTS) e del Comitato Prezzi e Rimborso (CPR) e metteranno la loro professionalità a disposizione del 'cuore' delle attività dell'Agenzia.

# Segretariati e Comitati Consultivi

- Per quanto riguarda i Comitati Consultivi, il loro compito sarà di effettuare approfondimenti e formulare pareri, in merito a questioni regolatorie e scientifiche di particolare interesse, su richiesta della CTS, del CPR o dei Segretariati.

- I Comitati sono costituiti da un massimo di sette componenti, selezionati tra i principali esperti clinici italiani di ciascuna area terapeutica indicata (al momento sono 6), che rispondono in pieno ai parametri stabiliti dal Regolamento sui conflitti di interesse approvato dall'AIFA nel gennaio del 2012.

# Segretariati e Comitati Consultivi

- In un'ottica di contenimento dei costi e snellimento delle procedure, ciascun Comitato si riunirà in modalità telematica (videoconferenza) e solo in occasioni di particolare importanza le riunioni avranno luogo presso la sede dell'AIFA. I membri dei Comitati Consultivi non hanno diritto ad alcun compenso ma, nel caso dei componenti provenienti da fuori Roma, al solo rimborso delle spese di viaggio.

- Il compito dei Segretariati di Supporto e Coordinamento, composti da un massimo di 10 membri, scelti tra personale AIFA (7) ed esperti presenti nella banca dati dell'Agenzia (per un massimo di 3), sarà quello di garantire un supporto ai lavori di CTS e CPR effettuando il raccordo con gli Uffici dell'AIFA e, qualora ve ne sia necessità, di richiedere approfondimenti e pareri ai Comitati Consultivi

# Amministrazione Trasparente

- Dati sulla trasparenza dell'azione amministrativa dell'Agenzia Italiana del Farmaco in osservanza al DLgs 33/2013 e successive modificazioni e alle altre norme vigenti.

- Responsabile della prevenzione della corruzione e della trasparenza (RPCT) (L. 190/2012).

- Informazioni sull'Agenzia Italiana del Farmaco

- Open Data: AIFA rende inoltre disponibili alcuni dati della sezione Amministrazione Trasparente anche in formato aperto e standardizzato per facilitarne la consultazione, il riutilizzo e la distribuzione. I dati sono accessibili sia nella sezione del portale dedicata che nelle pagine di riferimento.

**Direttore Generale**
Prof. Mario Melazzini
*Responsabile e Legale Rappresentante*

**Consiglio di Amministrazione**
Dr. Stefano Vella
*Presidente*

**Organismo Indipendente di Valutazione**
Sergio Basile
*Presidente*

**Collegio dei Revisori dei Conti**
Filippo D'Alterio
*Presidente*

**Ufficio di Presidenza**
Reggenza DG

**Area Relazioni Esterne**
Gianluca Polifrone

**Settore Affari Internazionali**
Gabriella Conti

**Area Legale**
Francesca Mastroianni
*ad interim*

**Settore ICT**
Reggenza DG

**Ufficio Qualità delle Procedure**
Reggenza DG

**Ufficio Controllo di Gestione**
Stefania Cuccagna

Data aggiornamento: settembre 2017

# Organizzazione AIFA

# Area Preautorizzazione

L'Area Pre-autorizzazione svolge le seguenti funzioni:

- coordinamento e supervisione delle attività afferenti ai medicinali sperimentali e alla ricerca clinica e interfaccia con altre Aree dell'Agenzia e con le altre istituzioni partecipanti al sistema della ricerca clinica nonché con le associazioni dei pazienti, ove ritenuto opportuno;
- normazione, linee guida e supporto regolatorio sulla sperimentazione e ricerca clinica;
- partecipazione ai processi di recepimento della normativa comunitaria e ai processi di normazione nazionale, in collaborazione con gli Uffici interessati e con il Ministero della Salute;

# Area Preautorizzazione

- formazione in materia di farmaci sperimentali e sperimentazione clinica, in cooperazione con gli Uffici dell'Area;
- promozione e supporto a investimenti in ricerca e sviluppo in Italia;
- coordinamento sezione del portale dell'Agenzia sulla sperimentazione clinica;
- redazione rapporti annuali sulle sperimentazioni cliniche;
- monitoraggio, gestione e accesso a farmaci sperimentali o off-label;
- gestione e monitoraggio richieste di autorizzazione all'impiego per terapie avanzate cellulari per uso nominale;
- coordinamento della partecipazione AIFA ai gruppi europei sulle sperimentazioni cliniche;
- gestione delle attività del gruppo di supporto per l'Area.

# Ufficio Ricerca Indipendente

L'Ufficio Ricerca Indipendente svolge le seguenti funzioni:

- predisposizione bandi per studi di ricerca sull'uso dei farmaci e sperimentazioni comparative tra farmaci tese a dimostrare il valore terapeutico aggiuntivo, ricerche su farmaci orfani e salvavita;

- individuazione progetti di ricerca destinatari del fondo di finanziamento dell'Agenzia;

- predisposizione di contratti per i progetti di ricerca pubblica finanziati da Agenzia;

# Ufficio Ricerca Indipendente

- supervisione tecnica ed amministrativa dei progetti di ricerca pubblica finanziati dall'Agenzia;
- predisposizione di indagini tecnico-scientifiche su aree e tematiche di interesse pubblico nel settore della ricerca clinica;
- predisposizione di rapporti di monitoraggio sull'efficacia dei progetti di ricerca pubblica finanziati dall'Agenzia

# Ufficio Sperimentazione Clinica

L'Ufficio Sperimentazione Clinica svolge le seguenti funzioni:

- gestione regolatoria, valutazione e autorizzazione delle sperimentazioni cliniche dalle fasi I alla fase IV in qualità di RMS e di CMS e dei relativi emendamenti sostanziali;

- gestione regolatoria e valutazione dei rapporti di sicurezza sulle sperimentazioni cliniche e delle segnalazioni di sicurezza per i farmaci sperimentali;

# Ufficio Sperimentazione Clinica

- gestione del portale e del database europeo per le sperimentazioni cliniche;
- gestione dell'Osservatorio nazionale sulle sperimentazioni cliniche;
- interazione con l'Istituto Superiore di Sanità e i Comitati etici, al fine della valutazione delle sperimentazioni cliniche;
- gestione registro studi osservazionali;
- gestione anagrafica e accreditamenti centri sperimentali, CRO e Comitati etici.

# L'Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali

- Un ruolo di particolare importanza riveste l'Osservatorio Nazionale sulla Sperimentazione Clinica dei medicinali (OsSC), coordinato e gestito direttamente dall'AIFA, strumento operativo previsto dalla normativa vigente per la gestione delle Sperimentazioni Cliniche (fase I-IV) che si svolgono in Italia e che funge anche da interfaccia per l'invio delle informazioni al database europeo EudraCT.

- L'Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali ha l'obiettivo di garantire la sorveglianza sulle Sperimentazioni Cliniche dei medicinali sperimentali condotte in Italia. L'OsSC raccoglie ed elabora i dati delle sperimentazioni e ne divulga i resoconti attraverso pubblicazioni periodiche, quale il Rapporto Nazionale sulla Sperimentazione Clinica in Italia.

# L'Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali

- Gli utenti abilitati (Promotori, CRO, Comitati Etici, ISS, AIFA) accedono all'OsSC tramite le credenziali rilasciate dall'Ufficio Sperimentazione Clinica dell'AIFA al fine di:

  – Preparare le domande per richiedere il parere del Comitato Etico e l'autorizzazione dell'Autorità Competente;
  – Comunicare le decisioni del Comitato Etico / Autorità Competente;
  – Notificare l'avvio, la conclusione e la pubblicazione dei risultati della sperimentazione.

# L'Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali

- Il supporto informativo dell'OsSC è costituito da registri informatizzati, predisposti in modo da essere compilati e consultati per via telematica da:
  - Comitati Etici;
  - Centri di Sperimentazioni Cliniche;
  - Centri e laboratori privati;
  - CRO autocertificate (ai sensi del Decreto Ministeriale 15 Novembre 2011);

# L'Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali

- Gli obiettivi principali dell'OsSC sono:
  - Armonizzazione delle procedure e delle documentazioni necessarie ad iniziare, emendare, concludere e riportare i risultati delle sperimentazioni;
  - Pubblicazione di rapporti annuali basati su dati nazionali e regionali rivolti agli operatori del settore e al pubblico in generale;
  - Realizzazione, d'intesa con le Regioni e le Province autonome, di iniziative di formazione.

# L'Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali

- Il sistema informativo dell'OsSC è inoltre caratterizzato da:
  - Adozione di livelli di sicurezza sulle informazioni e sull'accesso al sistema, a garanzia della riservatezza delle informazioni trattate;
  - Circolarità delle informazioni specifiche sulle sperimentazioni, limitatamente ai soggetti coinvolti.

# Le tappe miliari dell'OsSC

- Inizio operatività ad ottobre 2014 (base legale: Legge 189/2012, Art. 12, Comma 12, modalità di gestione dei flussi autorizzativi delle sperimentazioni cliniche telematica / e-submission)

- Avvio a doppia modalità (cartacea/telematica) fino a luglio 2015 in attesa del completamento del processo di ricostituzione dei Comitati etici (dopo luglio 2015 rimane la modalità cartacea in caso di coinvolgimento dei Comitati etici a carattere extra-territoriale/rilevanza nazionale)

# Le tappe miliari dell'OsSC

- Da ottobre 2015 sperimentazioni cliniche extra-sistema inserite in OsSC in occasione della sottomissione di un emendamento sostanziale

- Da febbraio 2016 emendamenti sostanziali in modalità cartacea in caso di malfunzionamenti/vincoli del sistema con ritorno delle relative sperimentazioni cliniche extra-sistema

- Da marzo 2017 rimappatura dei centri/Comitati etici della Regione Lombardia (a cui seguirà quella delle altre Regioni/Province autonome) e trasferimento telematico dei dati delle sperimentazioni cliniche da un Comitato etico ad un altro a seguito di cambi di competenza

# I Dati

- le anagrafiche degli utenti: Promotori n=763, CRO n=152 (italiane n=89, estere n=63), Comitati etici n=100+3

- le sperimentazioni cliniche e gli emendamenti sostanziali presentati all'AIFA: n=2199 (comprensive di quelle pregresse) e n=2174, rispettivamente

(al 20/02/2017)

# Sperimentazioni Cliniche via OsSC

| Anno | Sottomissioni |
|---|---|
| 2014 | 60 |
| 2015 | 876 |
| 2016 | 1177 |
| 2017 | 86 |
| TOT | 2199 |

(al 20/02/2017)

# Emendamenti Sostanziali via OsSC

| Anno | Sottomissioni |
|---|---|
| 2015 | 465 |
| 2016 | 1508 |
| 2017 | 201 |
| TOT | 2174 |

(al 20/02/2017)

# Criticità

- il mancato accesso delle Regioni/Province autonome in consultazione sui dati di propria competenza (le Regioni ricevono dal Richiedente quanto previsto dal DM 21.12.07, All.1, Parag.5 in accordo alla modalità transitoria http://www.agenziafarmaco.gov.it/sites/default/files/lettera_oggetto_sc_21_12_2012_0.pdf) (sviluppo in corso)

- l'assenza dello strumento di analisi e reportistica per Regioni/Province autonome e Comitati etici/Richiedenti relativamente ai dati delle sperimentazioni cliniche/emendamenti sostanziali di propria competenza (per le statistiche che ogni utenza potrebbe ottenere dalla propria sezione di OsSC) (sviluppo in corso)

# Criticità

- l'impossibilità di aggiornamento dell'anagrafica delle utenze (nuovo sviluppo in fase di implementazione)
- la funzionalità elettronica di delega Promotore-Richiedente (sviluppo in corso)
- la sequenzialità della sottomissione degli emendamenti sostanziali e la necessità di acquisizione di tutte le valutazioni dei CES a partire dal secondo emendamento sostanziale (sviluppo in corso)

# Valori aggiunti

- la gestione telematica di tutti i workflow di processo, compresa la documentazione (e-submission) … anticipazione del Portale EU

- la rete degli attori coinvolti (Richiedenti, CE, AC) facilitante la collaborazione dei CES con il CEC e nell'ottica dell'armonizzazione della documentazione centro specifica trasversale

# SPERIMENTAZIONE - 2015 - ITALIA
# 15° Rapporto nazionale - 2016

| | |
|---|---|
| 744 | • Nuove domande di sperimentazione |
| 672 | • Sperimentazioni autorizzate (90%) |
| 17,2% | • Italia/UE |


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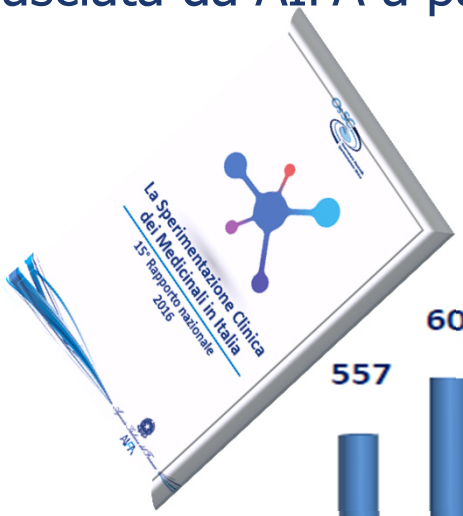
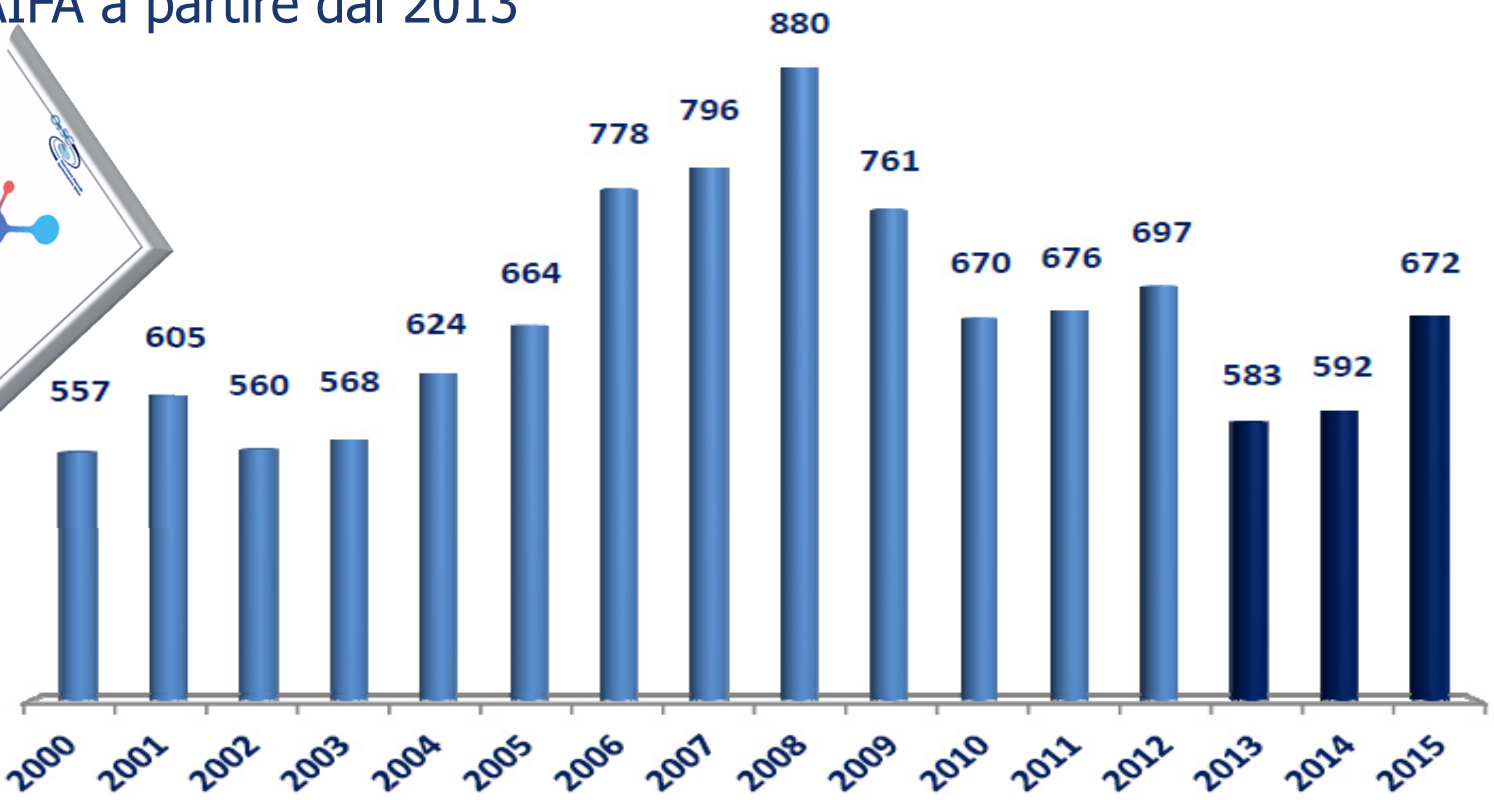
# 15° Rapporto nazionale - 2016

## Sperimentazioni Autorizzate dall' AC

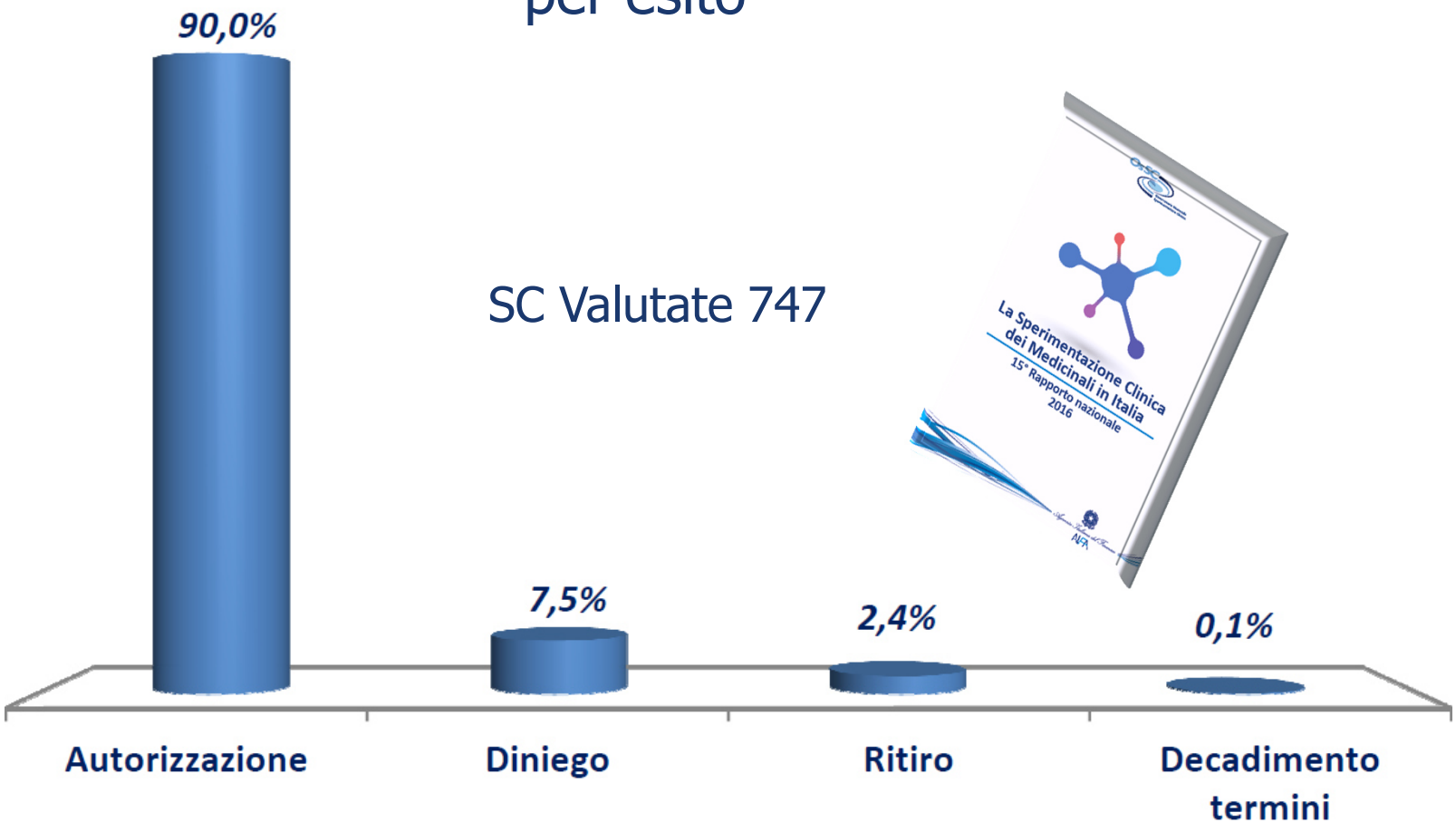
Parere unico favorevole rilasciato dal Comitato etico del centro coordinatore tra il 1° gennaio 2000 e il 31 dicembre 2012, contenute in OsSC, e autorizz. rilasciata da AIFA a partire dal 2013



# 15° Rapporto nazionale - 2016

## Sperimentazioni con iter autorizzativo concluso nel 2015 per esito




SC Valutate 747

# 15° Rapporto nazionale - 2016

## Sperimentazioni per anno: confronto Unione Europea – Italia

| Anno | SC in UE * | SC in Italia ** | % *Italia / UE* |
|---|---|---|---|
| 2011 | 4.127 | 676 | *16,4* |
| 2012 | 3.943 | 697 | *17,7* |
| 2013 | 3.383 | 583 | *17,2* |
| 2014 | 3.249 | 592 | *18,2* |
| 2015 | 3.918 | 672 | *17,2* |

Il numero di sperimentazioni cliniche nell'Unione Europea è stato ricavato dalle statistiche pubblicate sul sito EudraCT ("EudraCT supporting documentation" – "EudraCT statistics", *https://eudract.ema.europa.eu/statistics.html*).
Il numero di sperimentazioni cliniche in Italia è tratto dalla Tabella 4.

* numero di studi caricati nel sistema europeo
** numero di studi autorizzati dall'Autorità competente

# 15° Rapporto nazionale - 2016

| | |
|---|---|
| 43,6% | Fase I ( 10,3%) e II (33,3%) |
| 45,5% | Fase III – (Fase IV: 10,1%) |
| 64,4% | prodotti chimici |
| 31,5% | prodotti biologici/biotecnologici |
| 1,3% | prodotto chimico/biotecnologico |
| 2,7% | «ATIMP» |
| 16,8% | no profit |
| 24,9% | sperimentazioni in malattie rare |

Su 672 autorizzazioni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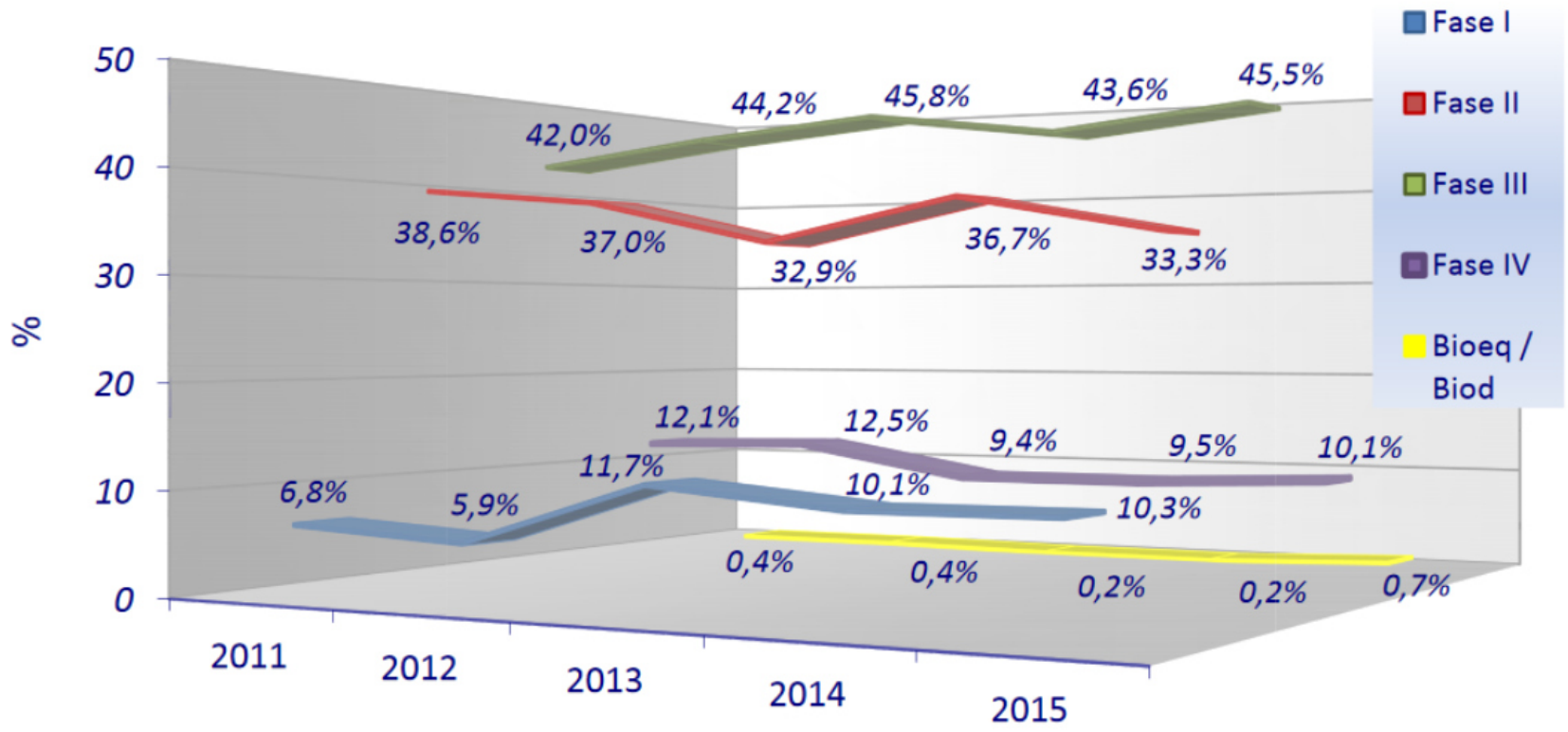
# 15° Rapporto nazionale – 2016

## Sperimentazioni per anno e fase

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# 15° Rapporto nazionale – 2016

## Sperimentazioni per classificazione terapeutica e fase

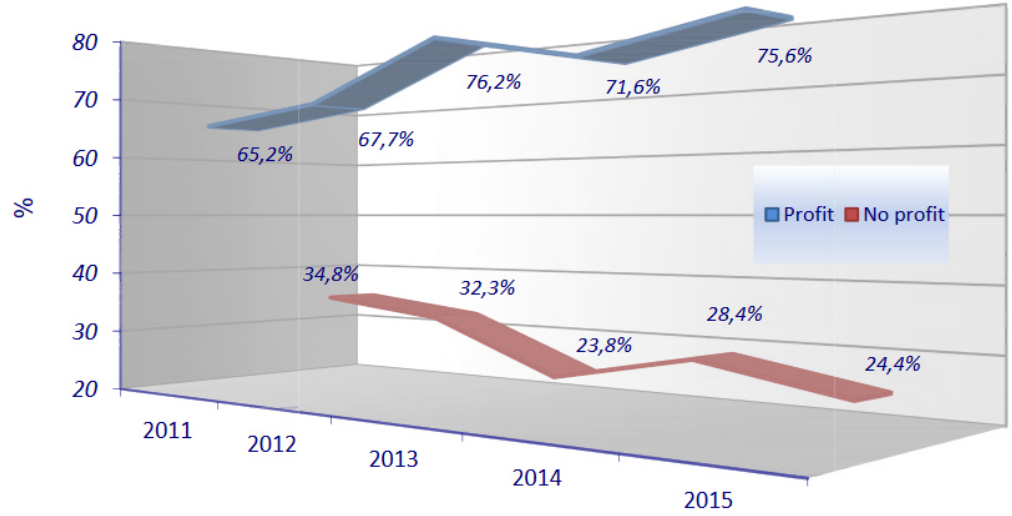
SC autorizzate nel 2015: 672 di cui 563 (83,8%) con ATC di almeno un farmaco in test specificato

| Classificazione terapeutica ATC 1° livello | | SC 2015 | % | Fase I | | Fase II | | Fase III | | Fase IV | | Bioeq / Biod | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | SC | % | SC | % | SC | % | SC | % | SC | % |
| L | Antineoplastici e immunomodulatori | **283** | ***47,6*** | 49 | *17,3* | 110 | *38,9* | 109 | *38,5* | 15 | *5,3* | 0 | *0,0* |
| J | Antimicrobici generali per uso sistemico | **51** | ***8,6*** | 2 | *3,9* | 13 | *25,5* | 25 | *49,0* | 9 | *17,6* | 2 | *3,9* |
| A | Apparato gastrointestinale e metabolismo | **46** | ***7,7*** | 1 | *2,2* | 16 | *34,8* | 20 | *43,5* | 8 | *17,4* | 1 | *2,2* |
| N | Sistema nervoso | **36** | ***6,1*** | 2 | *5,6* | 10 | *27,8* | 20 | *55,6* | 4 | *11,1* | 0 | *0,0* |
| B | Sangue e organi emopoietici | **34** | ***5,7*** | 6 | *17,6* | 9 | *26,5* | 14 | *41,2* | 5 | *14,7* | 0 | *0,0* |
| C | Sistema cardiovascolare | **27** | ***4,5*** | 1 | *3,7* | 9 | *33,3* | 16 | *59,3* | 1 | *3,7* | 0 | *0,0* |
| M | Sistema muscolo-scheletrico | **24** | ***4,0*** | 5 | *20,8* | 3 | *12,5* | 12 | *50,0* | 3 | *12,5* | 1 | *4,2* |
| V | Vari | **24** | ***4,0*** | 0 | *0,0* | 8 | *33,3* | 11 | *45,8* | 5 | *20,8* | 0 | *0,0* |
| H | Preparati ormonali sistemici, esclusi ormoni sessuali | **20** | ***3,4*** | 3 | *15,0* | 8 | *40,0* | 6 | *30,0* | 3 | *15,0* | 0 | *0,0* |
| R | Sistema respiratorio | **18** | ***3,0*** | 1 | *5,6* | 3 | *16,7* | 11 | *61,1* | 3 | *16,7* | 0 | *0,0* |
| S | Organi di senso | **15** | ***2,5*** | 0 | *0,0* | 4 | *26,7* | 6 | *40,0* | 5 | *33,3* | 0 | *0,0* |
| G | Sistema genito-urinario e ormoni sessuali | **8** | ***1,3*** | 0 | *0,0* | 1 | *12,5* | 6 | *75,0* | 1 | *12,5* | 0 | *0,0* |
| D | Dermatologici | **7** | ***1,2*** | 2 | *28,6* | 0 | *0,0* | 5 | *71,4* | 0 | *0,0* | 0 | *0,0* |
| P | Antiparassitari, insetticidi e repellenti | **1** | ***0,2*** | 0 | *0,0* | 0 | *0,0* | 1 | *100,0* | 0 | *0,0* | 0 | *0,0* |
| | **Totale** | **594** | ***100,0*** | **72** | ***12,1*** | **194** | ***32,7*** | **262** | ***44,1*** | **62** | ***10,4*** | **4** | ***0,7*** |

# 15° Rapporto nazionale – 2016

## Sperimentazioni per anno e promotore profit/no profit

| Anno | Profit | | No profit | | Totale | |
|---|---|---|---|---|---|---|
| | SC | % | SC | % | SC | % |
| 2011 | 441 | *65,2* | 235 | *34,8* | **676** | ***100,0*** |
| 2012 | 472 | *67,7* | 225 | *32,3* | **697** | ***100,0*** |
| 2013 | 444 | *76,2* | 139 | *23,8* | **583** | ***100,0*** |
| 2014 | 424 | *71,6* | 168 | *28,4* | **592** | ***100,0*** |
| 2015 | 508 | *75,6* | 164 | *24,4* | **672** | ***100,0*** |
| **Totale** | **2.289** | ***71,1*** | **931** | ***28,9*** | **3.220** | ***100,0*** |

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# 15° Rapporto nazionale - 2016

## Sperimentazioni in malattie rare

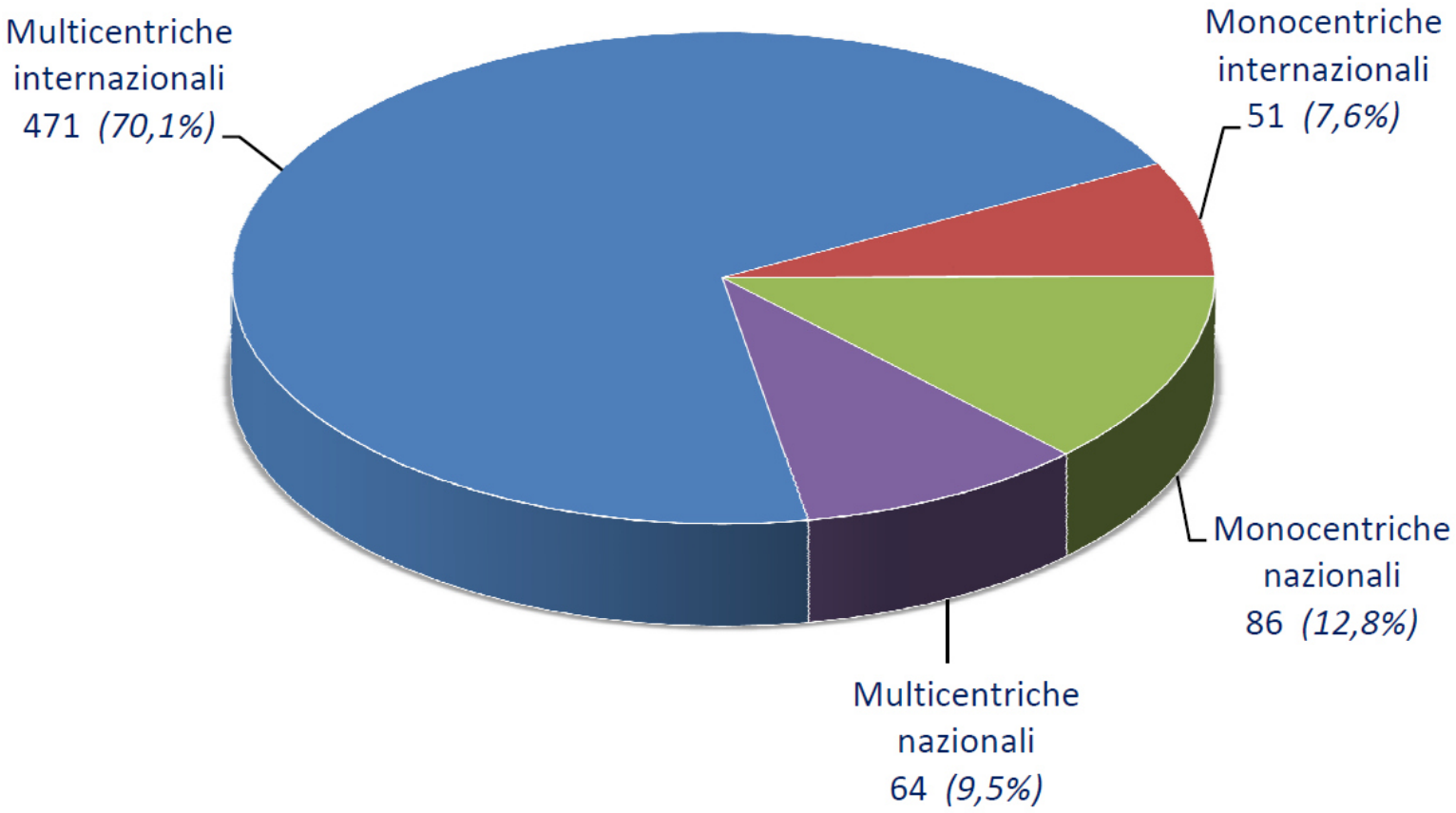
**Sperimentazioni in malattie rare per Promotore profit/no profit, nazionali e internazionali**

**SC autorizzate nel 2015: 24,9% in malattie rare (167 su 672)**

| Tipo Promotore | Nazionali SC (%) | Internazionali SC (%) | Totale SC (%) |
|---|---|---|---|
| Profit | 4,8% | 94,5% | 83,2% |
| No profit | 95,2% | 5,5% | 16,8% |
| TOTALE | 12,6% | 87,4% | 100,0% |

# 15° Rapporto nazionale - 2016

## Sperimentazioni monocentriche e multicentriche, nazionali e internazionali



# 15° Rapporto nazionale - 2016

## Mercati Farmaceutici Mondiali - 2015


| Paesi | Valori a ricavo industria (mln di euro) | % |
|---|---|---|
| USA | 334.167 | *40,3* |
| Giappone | 65.853 | *7,9* |
| **Paesi Big UE** | **129.964** | ***15,7*** |
| Germania | 35.298 | *4,3* |
| Francia | 28.951 | *3,5* |
| **Italia** | **24.290** | ***2,9*** |
| Regno Unito | 23.144 | *2,8* |
| Spagna | 18.281 | *2,2* |
| **Paesi BRIC** | **103.138** | ***12,4*** |
| | ≈ | |
| **Totale Mondo** | **829.727** | ***100,0*** |

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# 15° Rapporto nazionale - 2016

## Investimenti e addetti in ricerca e sviluppo nell'industria farmaceutica


| Paesi | | Investimenti (milioni di euro) | % | Addetti | % |
|---|---|---|---|---|---|
| Germania | | 5.813 | *24,2* | 19.259 | *19,1* |
| Regno Unito | | 4.868 | *20,3* | 24.000 | *23,8* |
| Francia | | 4.564 | *19,0* | 20.054 | *19,9* |
| **Italia** | **2014** | **1.350** | ***5,6*** | **5.950** | ***5,9*** |
| | **2015** | **1.415** | ***/ **** | **6.100** | ***/ **** |
| Spagna | | 953 | *4,0* | 5.116 | *5,1* |
| **Paesi Big UE 5** | | **17.548** | ***73,0*** | **74.379** | ***73,9*** |
| **Paesi UE** | | **24.036** | ***100,0*** | **100.637** | ***100,0*** |

* dati non ancora disponibili alla data di pubblicazione del Rapporto OsSC

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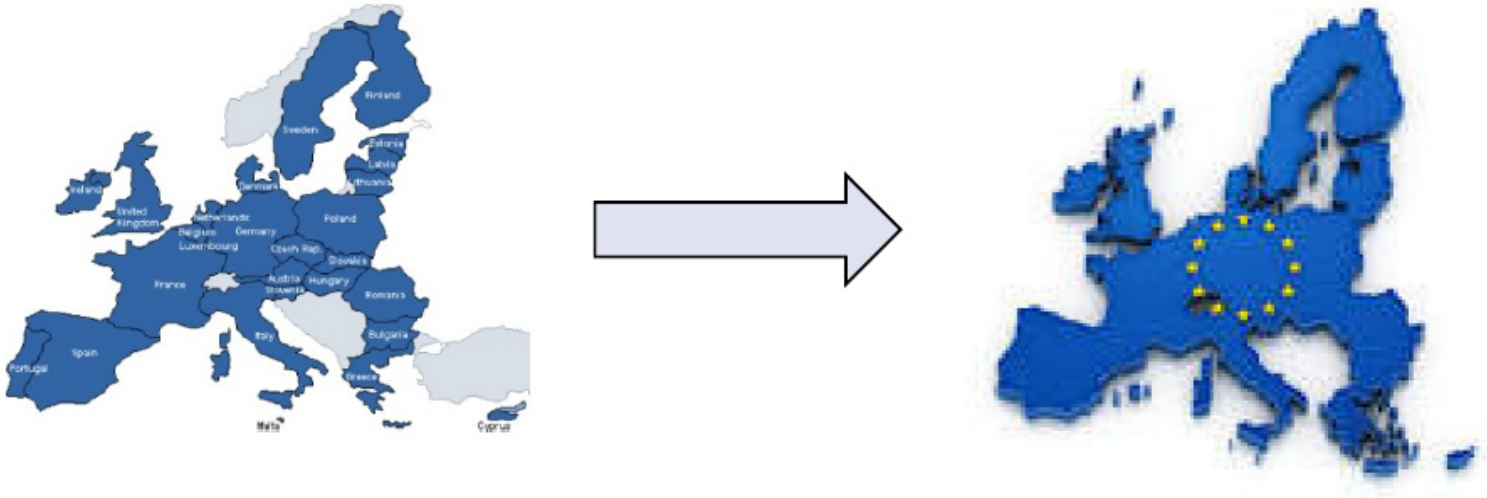
# Il Nuovo Regolamento (UE) n. 536/2014

Regolamento (UE) n. 536/2014 del Parlamento europeo e del Consiglio, del 16 aprile 2014, sulla sperimentazione clinica di medicinali per uso umano e che abroga la direttiva 2001/20/CE




D.L. 24 giugno 2003, n. 211
Direttiva 2001/20/CE

Regolamento (UE) n. 536/2014

# Agenda

- Introduction and overview
- Submission initial application and substantial modifications
- Content of an application
- Safety – GCP – Protection of Subjects and ICF
- Manufacturing Importation and Labeling
- Summary & Impact on MS

# Introduction and overview

# Directive 2001/20 EC

- Pre May 2004: Differences in approval procedures and laws relating to clinical trials within the EU. Achieving consistent approvals of trials was challenging.

- Harmonised approach necessary for initiation, conduct and monitoring of trials = "Clinical Trials Directive 2001/20/EC"

Transposed into national law in each Member State

# Aims of Directive 2001/20 EC

- The protection of the health and safety of clinical trial participants
- The ethical soundness of the clinical trial
- The reliability and robustness of data generated in clinical trials
- Simplification and harmonisation of the administrative provisions governing clinical trials in order to allow for cost-efficient clinical research

- *This "should be achieved while promoting high-quality research in the EU and the competitiveness of the European pharmaceutical industry."*

- Did the Directive met its objectives?

# Why change from the Directive?

- *Improvements in the safety and ethical soundness of clinical trials in the EU and in the reliability of clinical trials data. Also increased cooperation between MS; however….*
  - Decrease in EU CTAs (2007-2011)
  - Increase in costs
  - Increase in delay to trial initiation
  - Different requirements in different MS

- Not all because of Directive 2001/20/EC but it is *"Arguably the most heavily criticised piece of EU-legislation in the area of pharmaceuticals."* (European Commission)

# Revision of the Directive 2001/20 EC

- Dec 2008: Commission announces that an assessment would be made of the application of the Clinical Trials Directive
- Oct 2009: Public consultation on the functioning of the Directive
- Feb 2011: Concept Paper on revision of the Clinical Trials Directive published for Public consultation
- Jul 2012: Proposal for a Regulation and repealing Directive
- Dec 2013: Informal agreement on text
- Apr 2014: Plenary vote in Parliament: 594 votes to 17 in favour, with 13 abstentions
- April 2014: Approved in Council
- May 2014: Published in Official Journal by Commission
- Jun 2014: Entered into force

# Overview of the Regulation

- It is a Regulation!

Directives

- Binding legal requirements which are met by each Member State passing national legislation.

Regulations

- Binding in their entirety and become directly applicable to all Member States, without having to pass separate national legislation

# Overview of the Regulation

- Scope: The scope of the legislation has not greatly changed. It still applies only to interventional studies of medicinal products. HOWEVER, introduces the concept of 'low-intervention trials'. Also NIMPs (now auxiliary medicinal products) are within scope of the regulation.

- Major advantages are the streamlined submission and review process for trial applications via the EU portal and database, enhanced communication and cooperation between Member States, simplified safety reporting, increased transparency

# Scope

This Regulation applies to all clinical trials conducted in the Union.
It does not apply to non-interventional studies.

CAPO I

**DISPOSIZIONI GENERALI**

*Articolo 1*

**Ambito di applicazione**

Il presente regolamento si applica a tutte le sperimentazioni cliniche condotte nell'Unione.

Esso non si applica agli studi non interventistici.

# Definitions – Clinical Study

*Articolo 2*

**Definizioni**

1. Ai fini del presente regolamento si applicano le definizioni di «medicinale», «radiofarmaco», «reazione avversa», «reazione avversa grave», «confezionamento interno» e «confezionamento esterno» di cui all'articolo 1, rispettivamente punti 2, 6, 11, 12, 23 e 24 della direttiva 2001/83/CE.

2. Ai fini del presente regolamento si applicano inoltre le seguenti definizioni:

1) «studio clinico»: qualsiasi indagine effettuata in relazione a soggetti umani volta a:

a) scoprire o verificare gli effetti clinici, farmacologici o altri effetti farmacodinamici di uno o più medicinali;

b) identificare eventuali reazioni avverse di uno o più medicinali; oppure

c) studiare l'assorbimento, la distribuzione, il metabolismo e l'eliminazione di uno o più medicinali,

al fine di accertare la sicurezza e/o l'efficacia di tali medicinali;

# Definitions – Clinical Trial

2) «sperimentazione clinica»: uno studio clinico che soddisfa una delle seguenti condizioni:

   a) l'assegnazione del soggetto a una determinata strategia terapeutica è decisa anticipatamente e non rientra nella normale pratica clinica dello Stato membro interessato;

   b) la decisione di prescrivere i medicinali sperimentali e la decisione di includere il soggetto nello studio clinico sono prese nello stesso momento; o

   c) sono applicate ai soggetti procedure diagnostiche o di monitoraggio aggiuntive rispetto alla normale pratica clinica;

# DEFINIZIONI STUDI

3) «sperimentazione clinica a basso livello di intervento»: una sperimentazione clinica che soddisfa tutte le seguenti condizioni:

a) i medicinali sperimentali, ad esclusione dei placebo, sono autorizzati;

b) in base al protocollo della sperimentazione clinica,

i) i medicinali sperimentali sono utilizzati in conformità alle condizioni dell'autorizzazione all'immissione in commercio; o

ii) l'impiego di medicinali sperimentali è basato su elementi di evidenza scientifica e supportato da pubblicazioni scientifiche sulla sicurezza e l'efficacia di tali medicinali sperimentali in uno qualsiasi degli Stati membri interessati; e

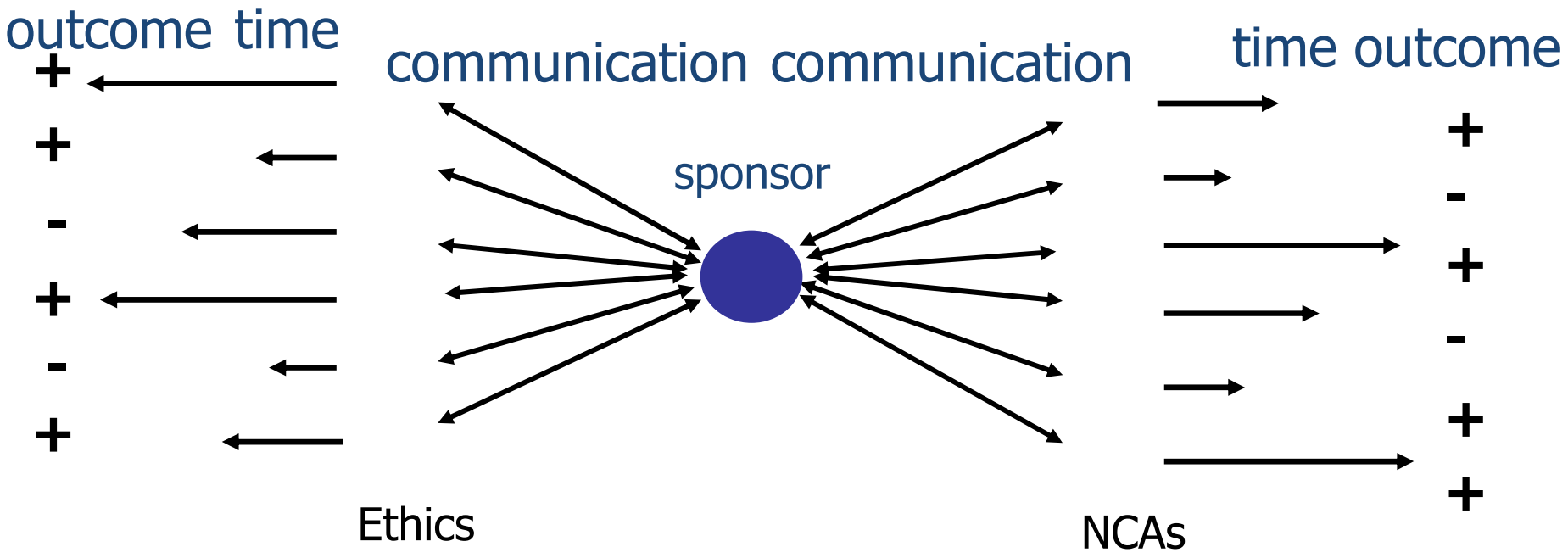
c) le procedure diagnostiche o di monitoraggio aggiuntive pongono solo rischi o oneri aggiuntivi minimi per la sicurezza dei soggetti rispetto alla normale pratica clinica in qualsiasi Stato membro interessato;

4) «studio non interventistico»: uno studio clinico diverso da una sperimentazione clinica;

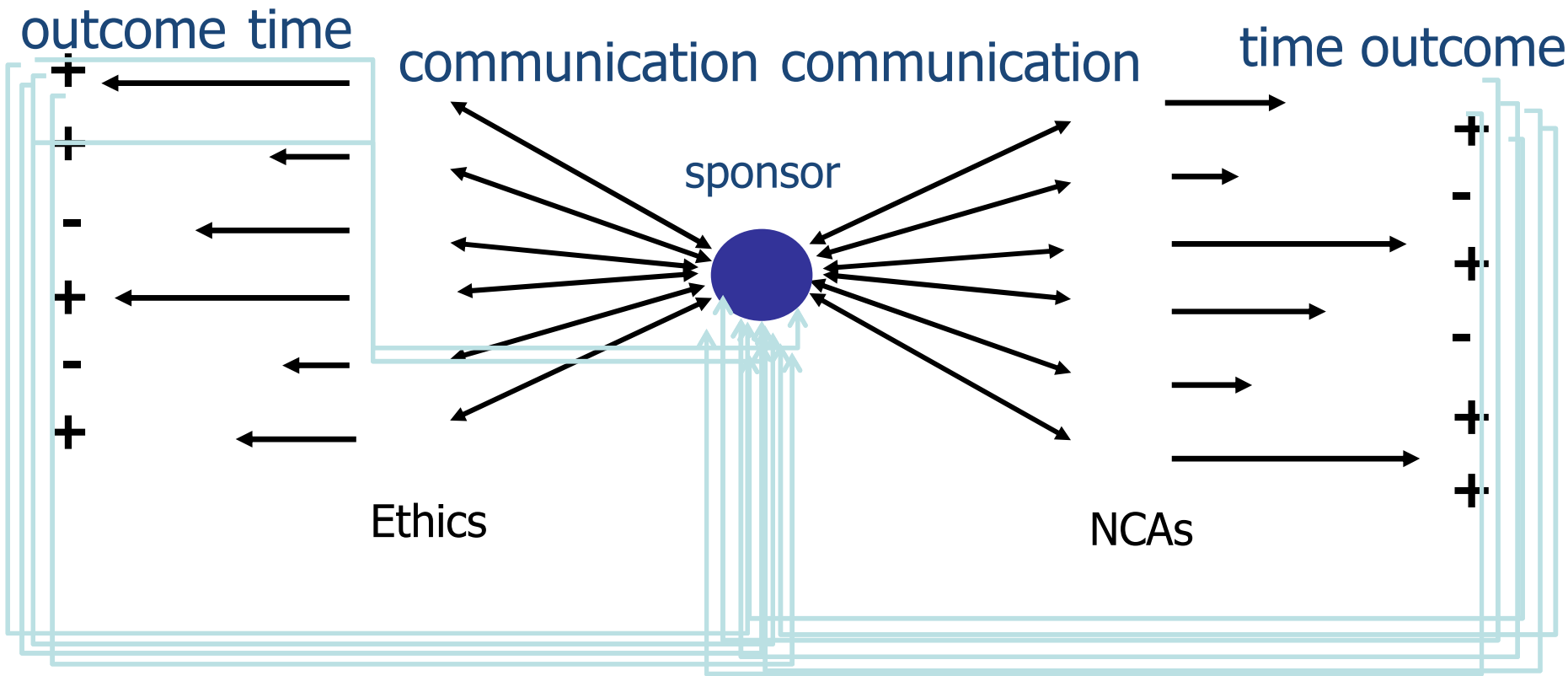
# New simplified approval procedure

- Single EU Portal & Database
- Single dossier and single submission
- Sponsor can propose Reporting MS
- Coordinated assessment for multi-state clinical trials
  - Part I – joint assessment by all concerned MS (NCA+EC), led by RMS
  - Part II – National assessment only (R&D offices and Ethics Committee)
- Clear timelines (extended compared with Directive), concept of tacit approval

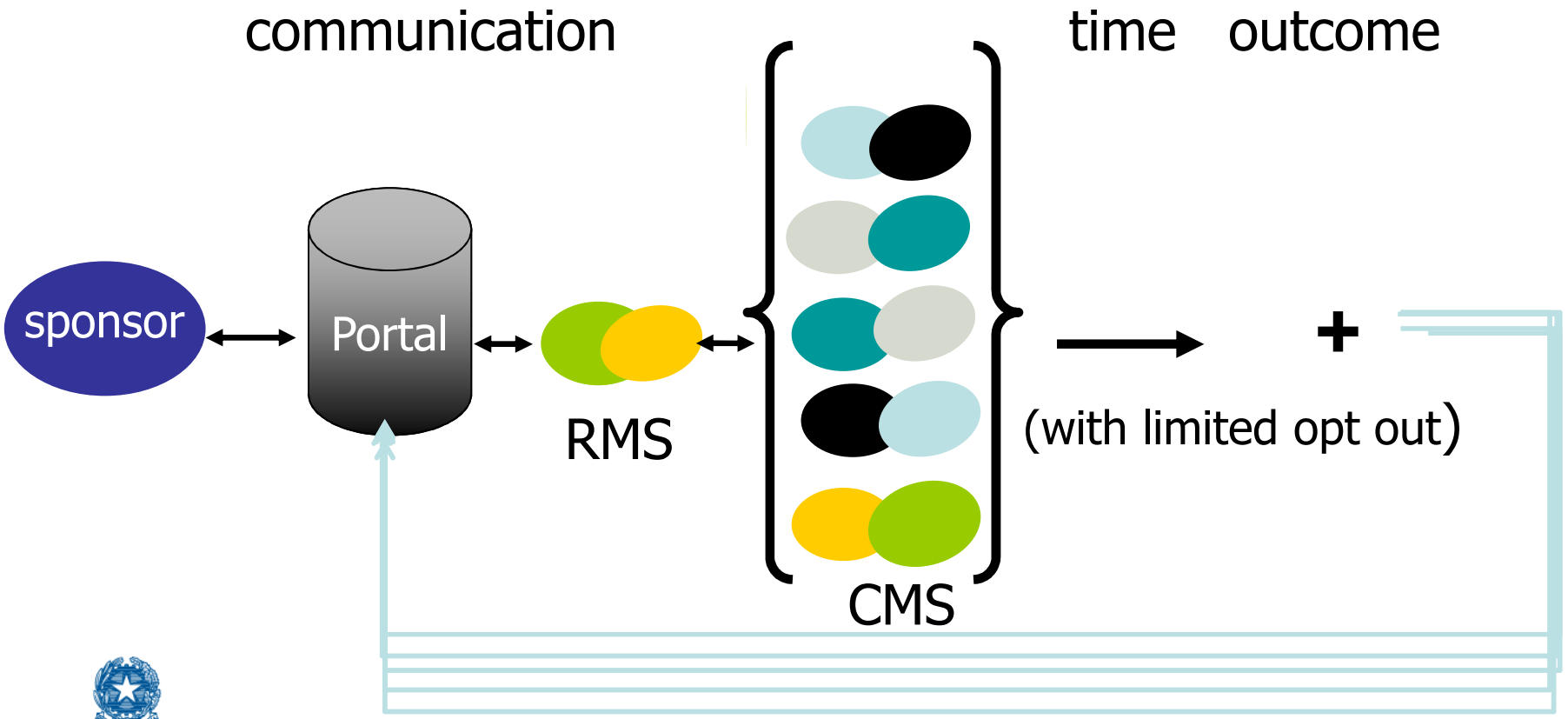
# EU Multi-national clinical trials: current situation



# EU Multi-national clinical trials: current situation



# EU Multi-national clinical trials: under new Regulation



# Transparency

- The Regulation requires that information contained in the clinical trial database shall be publicly available unless one or more of the following exceptions apply:
- protection of personal data;
- protection of commercially confidential information, in particular taking into account the marketing authorisation status of the medicinal product, unless there is an overriding public interest;
- protection of confidential communication between Member States in the preparation of their assessment;
- protection of the supervision of clinical trials by Member States

# Transparency

- Disclosure rules published in October 2015: EMA/42176/2014
- Includes descriptions of what and when documents may be made public depending on stage of development, type of trial (therapeutic vs non-therapeutic) and type of document. Publication rules based on three categories of trials
    - Category 1: Phase 1, bioequivilance / bioavailability / biosimilar trials
    - Category 2: Phase II and III (ie not Cat 1 or 3)
    - Category 3: Phase IV and low-intervention trials
- *Provides balance between encouraging innovation and providing extensive public information on clinical trials conducted in EU.*

# EU and National implementation

- At EU and National levels work falls broadly into three categories:

1. IT systems & process development

2. Development of supporting legislation / guidance

3. Communications & training

# IT systems and process development

- Recital "…the Agency should, in collaboration with Member States and the Commission, set up and maintain an EU database, accessed through an EU portal."

- Article 80: "The Agency shall, in collaboration with the Member States and the Commission, draw up the functional specifications for the EU portal and the EU database, together with the time frame for their implementation."

# IT systems and process development

EU clinical trials information system expert group

MS represented at face-to-face meetings and also subgroup teleconferences.

Number of subgroups:

- Sponsor driven activities
- Member State driven activities
- Inspections
- User access
- Public view

# IT systems and process development

- In parallel to the portal & database, other EMA teams working on:
  - SUSAR reporting tool
  - Annual Safety report database
  - Data-warehouse capability
  - Substance/Product dictionary for IMPs
  - EudraCT and EU CT Registry legacy processes
- It is expected timelines for implementation for all will be the same

# IT systems and process development

- National IT systems development
- EU Portal and Database will not facilitate workflows at a national level therefore some countries will also develop their own IT systems to assist work management
- May depend on functionality offered in portal and database
- May depend on the number of trials for that MS

# Supporting Legislation / Guidance

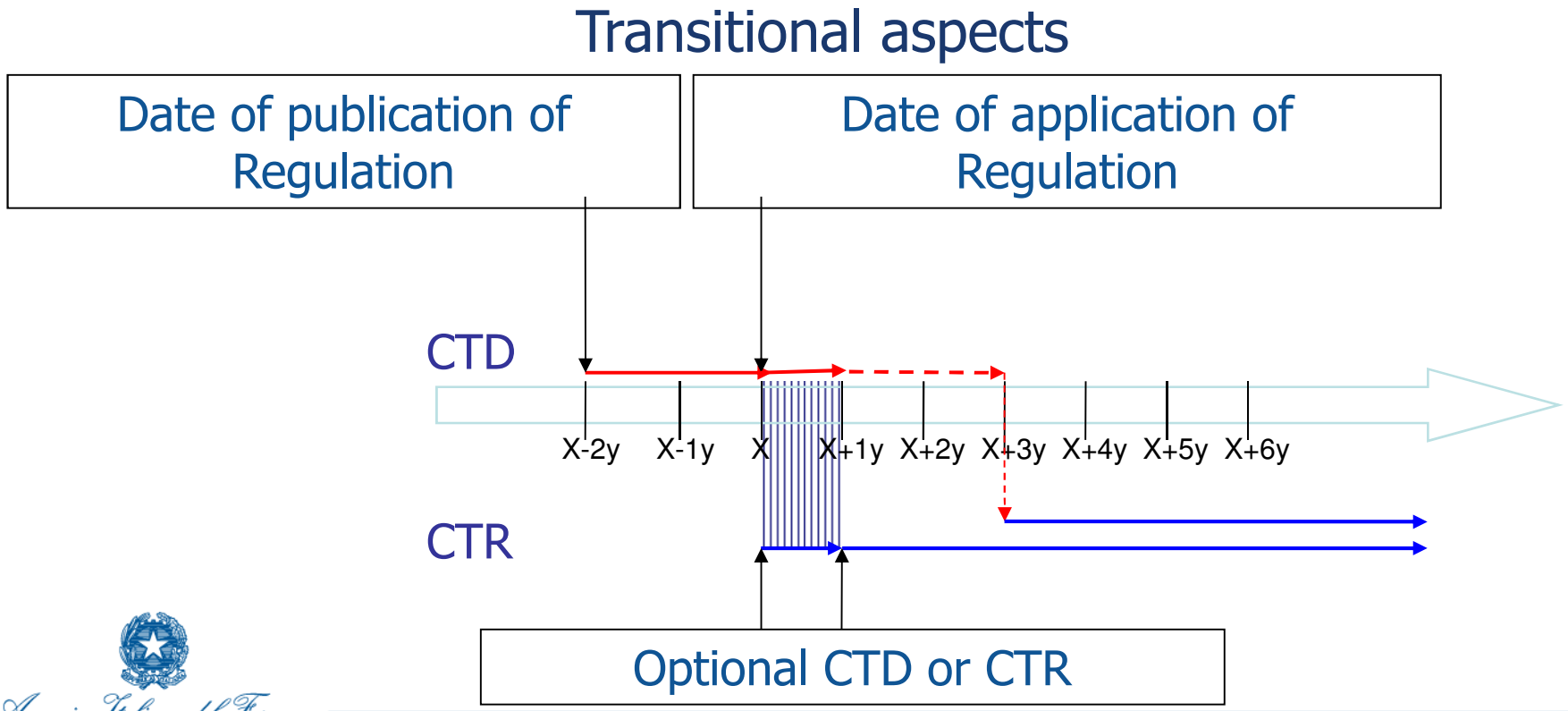
- EU
  - Delegated act (GMP),
  - Implementing acts (modalities for inspection, collaboration on assessment of safety data)
  - Guidance documents: Q&As; AMPs, risk proportionality
- National
  - (re)Establish and define role of ethics committees
  - Appeal mechanisms
  - Informed consent – interviews, cluster trials
  - Minors / incapacitated subjects
  - Fees

# Communication and Training

- EU
  - CTFG working with EU Network Training Centre to roll out a training program for MS
  - Possibility of beta version of portal and database for training and process development
- National
  - National communication plans to support local research community
  - Many MS have instigated pilot programs

# When will the Regulation come into Force?

Article 99 shall apply "no earlier than 28th May 2016" (6 months after successful audit of IT system). Now expected during 2019?



## Implementation (updated)

Although the Regulation was adopted and entered into force in 2014, the timing of its application depends on **confirmation of full functionality** of the EU portal and database through an independent audit. The Regulation becomes applicable six months after the European Commission publishes notice of this confirmation.

EMA's Management Board endorsed a delivery timeframe in December 2015. However, due to technical difficulties with the development of the IT systems, the portal's go-live date has to be **postponed**.

EMA's Management Board will discuss a **new delivery time frame** in October 2017 once the developer confirms progress.

Due to these delays, the **EU Clinical Trial Regulation** will come into application during 2019 instead of October 2018, as previously scheduled.

For more information on the original delivery timeframe, see:

- Delivery time frame for the EU portal and EU database

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp

# Summary

- Regulation 536/2014 addresses the concerns experienced with Directive 2001/20 EC
- For sponsors - a more streamlined, efficient and consistent regulatory environment
- For regulators – work-sharing, improved working practices, single IT system, (but more complex interactions)
- Potentially much greater interactions between NCAs and ethics
- Potential is great if we get it right!

# Submission of an initial application and assessment

# Overview

- Introduction & abbreviations
- General principles
- Submission
- RMS selection
- Assessment part I & II
- Decision
- Specific articles (9-13)
- Addition of a memberstate
- Challenges

# Submission of initial application

CHAPTER II

**AUTHORISATION PROCEDURE FOR A CLINICAL TRIAL**

Articles 4 – 14 cover the submission of an initial application

# Abbreviations

- AR – Assessment Report
- CTA – Clinical Trial Application
- CTR – Clinical Trial Regulation
- MSC – Member State Concerned (i.e. member state where the trial will be performed that does not act as RMS)
- NCA – National Competent Authority
- RMS – Reporting Member State

# Article 4 - Prior authorisation

- A clinical trial shall be subject to scientific and ethical review
- Ethical review :
  - Is performed by an ethics committee
  - Member states need to ensure that timelines & procedures for ethics committees are feasible
- National law needs to determine the exact role of Ethics committees and National Competent Authorities in part I and part II (see further)

# General principles - Submission and assessment

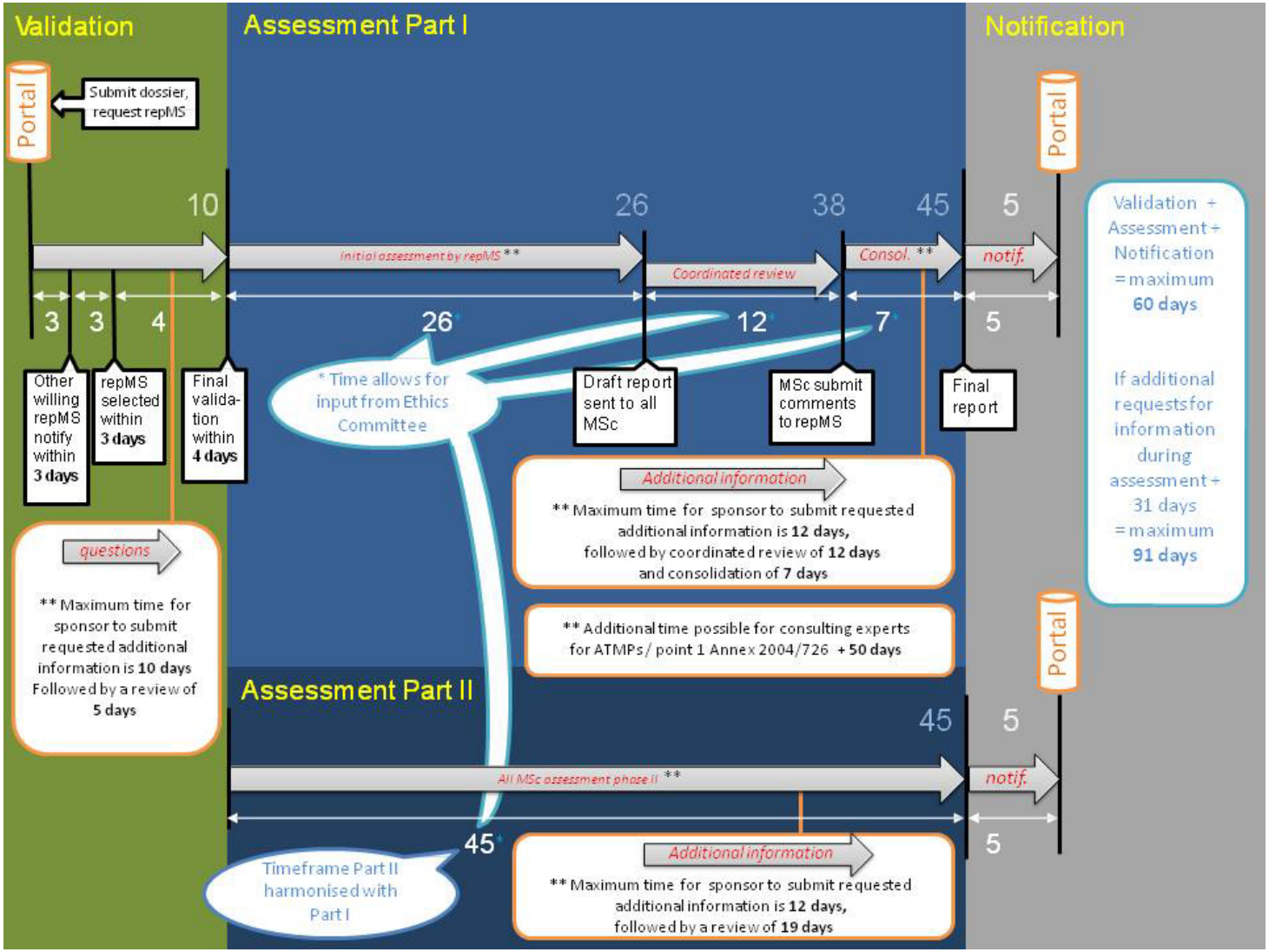
- The RMS drives the assessment process for those aspects that are considered to be scientifically harmonized within the EU (PART I)
- Each MSC assesses the aspects that are of a more national/local nature (PART II)
- Both parts constitute the assessment report and need to comply to the applicable rules in the CTR
- The member state needs to define the exact roles of ethics committee(s) and NCA(s) – the legal text focusses on the member state responsibilities

# Timelines and delays (1)

- Timelines in the CTR are calendar days
- Timelines are maximum timelines, so they can be shortened
- A clock stop between 23rd December to 7th January (for all clinical trials i.e. national and multinational) will exist
- The reference time zone is Central European Time (« Brussels time »)
- Tacit approval system is in place for the validation and submission processes

# Timelines and delays (2)

- Regulation 1182/71 defines how timelines should be calculated for legally defined delays
- Where the last day of a period expressed otherwise than in hours is a public holiday, Sunday or Saturday, the period shall end with the expiry of the last hour of the following working day.
- Any period of two days or more shall include at least two working days.

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# Article 5 – Submission of an application

- Submission of an application dossier through the EU Portal by the sponsor
- Sponsor needs to propose a RMS
- Specific procedure set up to establish the RMS for multinational trials
- Application dossier defined in annex I of the CT
- Validation process to be done by RMS

# Initial trials : submission and validation (1)

- D0: submission of the application dossier to the EU Portal. One of the MSC is proposed as the RMS
- D+6 : RMS is selected and notified to the sponsor (see further)
- D+7 : CMS may communicate considerations on validation to the RMS
- D+10 : RMS notifies whether the CT falls within the scope of the CTR and whether the application dossier is complete (“valid application”)
- When the application is not valid, the RMS informs the sponsor

# Initial trials : submission and validation (2)

- Sponsor to comment or complete the application within 10 days
- If the sponsor has not provided a response within this timeline, the application is considered to be lapsed
- Upon receipt of the answer, the RMS has 5 days to declare the dossier valid or not
- When the RMS does not respect the timeline, the application is considered to be complete and falling within the scope of the CTR
- The date on which the sponsor is notified of a valid dossier is the validation date of the dossier.

# Initial trials : submission and validation (3)

- Calendar calculation for multinational applications :
- Up to day 3- The calendar of the MSC with the longest calendar will be used
- Day 4 to 6- the calendar will be as follows:
  - 1- The system will identify which is the MSC with the longest calendar from day 4 to 6 and identify the dates for day 4 and 6
  - 2- The system will sum the holidays of all the MSC from the date of day 4 to the date of day 6
- The calendar of the RMS will be used from day 7 onwards

# RMS selection process (1)

- All MSC can express willingness within 3 days after submission
- Depending on the first step, 4 scenarios are possible :

  - Only the memberstate proposed by the sponsor is willing □ RMS as proposed by the sponsor
  - Only 1 MSC is willing □ this CMS will be RMS

  - No MSC are willing □ worksharing algorithm
  - Multiple MSC are willing □ worksharing algoritm

# RMS selection process (2)

- Worksharing algorithm calculates the percentage of multinational trials where a member state acts as RMS :

$$x\,\% = \frac{\text{number of multinational clinical trials where the Member State acts as RMS}}{\text{total number of multinational trials where the Member State participates}} * 100$$

- In general, the rule is that the member state with the lowest % takes up the RMS-ship
- In some cases, it might be logical to deviate from that rule, but this should be discussed in a transparent way
- If no consensus is reached on day 6, the RMS proposed by the sponsor will be maintained.

And what about MS Resources ???

# Article 6 – Assessment report – Part I (1)

- RMS assesses the aspects of part I, generates an assessment report (AR), and formulates a conclusion (acceptable, acceptable with conditions, not acceptable)
- For multinational trials, this happens in 3 phases :
    - Initial assessment phase (drafting of the AR by the RMS)
    - Coordinated review phase (all member states review the draft AR and share their considerations)
    - Consolidation phase (consolidation of the considerations in a final part I AR)
- RMS can request for additional information on part I

# Article 6 – Assessment report – Part I (2)

- Aspects of part I :

  (a) Low-intervention clinical trial or not

  (b) Compliance to chapter V with regard to the benefits (IMP, relevance, reliability of the data) and the risks (IMP, AMP, comparison with normal clinical practice, safety measures, risk of the medical condition) of the trial

  (c) Manufacturing & import of IMP & AMP (chapter IX)

  (d) Labelling requirements (chapter X)

  (e) Completeness & adequateness of the Investigators Brochure

# Initial trials process : assessment of part I (1)

- D0: validation date of the application
- D+26: draft Part I AR made available by the RMS (initial assessment phase)
  - End of initial assessment phase + 12 : all CMS can share considerations (coordinated review phase) (38)
    - End of coordinated review phase + 7 : RMS finalizes the Part I AR (consolidation phase) (45)
- D+45 : final assessment report from the RMS submitted to the EU Portal – this date is the reporting date

# Initial trials process : assessment of part I (2)

- The RMS can request additional information from the sponsor between validation date and reporting date – timeline is extended with 31 days
- Sponsor submits the additional information within 12 days
- The answer is jointly reviewed by all CMS, considerations are shared within 12 days
- Final consolidation by the RMS within 7 days.
- If the sponsor has not provided a response within the timeline, the application is considered to be lapsed
- Calendar is the same for all MSC and is based on the RMS's public holidays

# Article 7 – Assessment report – Part II (1)

- All MSC assess (for their own territory), the aspects of part II, generate a part II AR, and formulate a conclusion

- Aspects of part II :

(a) Requirements for informed consent (chapter V)

(b) Compensation of subjects and investigators

(c) Recruitment arrangements

- … continued on the next slide…

# Article 7 – Assessment report – Part II (2)

- Aspects of part II (continued):

- (d) Compliance with the rules on data protection
- (e) Suitability of individuals involved in the conduct of the trial
- (f) Suitability of the clinical trial sites
- (g) Damage compensation
- (h) Collection, storage and future use of biological samples

# Initial trials process : assessment of part II (1)

- D0: validation date of the application
- D+45 : final assessment report from each MSC submitted
- All MSC can request additional information from the sponsor between validation date and reporting date – timeline is extended with 31 days
- Sponsor submits the additional information within 12 days
- Final assessment by the MSC shall be performed within 19 days.
- If the sponsor has not provided a response within the timeline, the application is considered to be lapsed
- Calendar calculation is based on each MSC's calendar

# Article 8 – Decision (1)

- One single decision (part I + II) per member state
- For a CMS, the Part I decision is the conclusion of the RMS, except when :
  - Subjects receive inferior treatment compared to the normal clinical practice in that member state
  - Specific rules in national legislation are not met
  - Considerations on safety or reliability that were shared during the coordinated review phase remain
- Disagreement with the Part I decision of the RMS needs to be communicated through the EU Portal and justified

- One single decision (part I + II) per member state

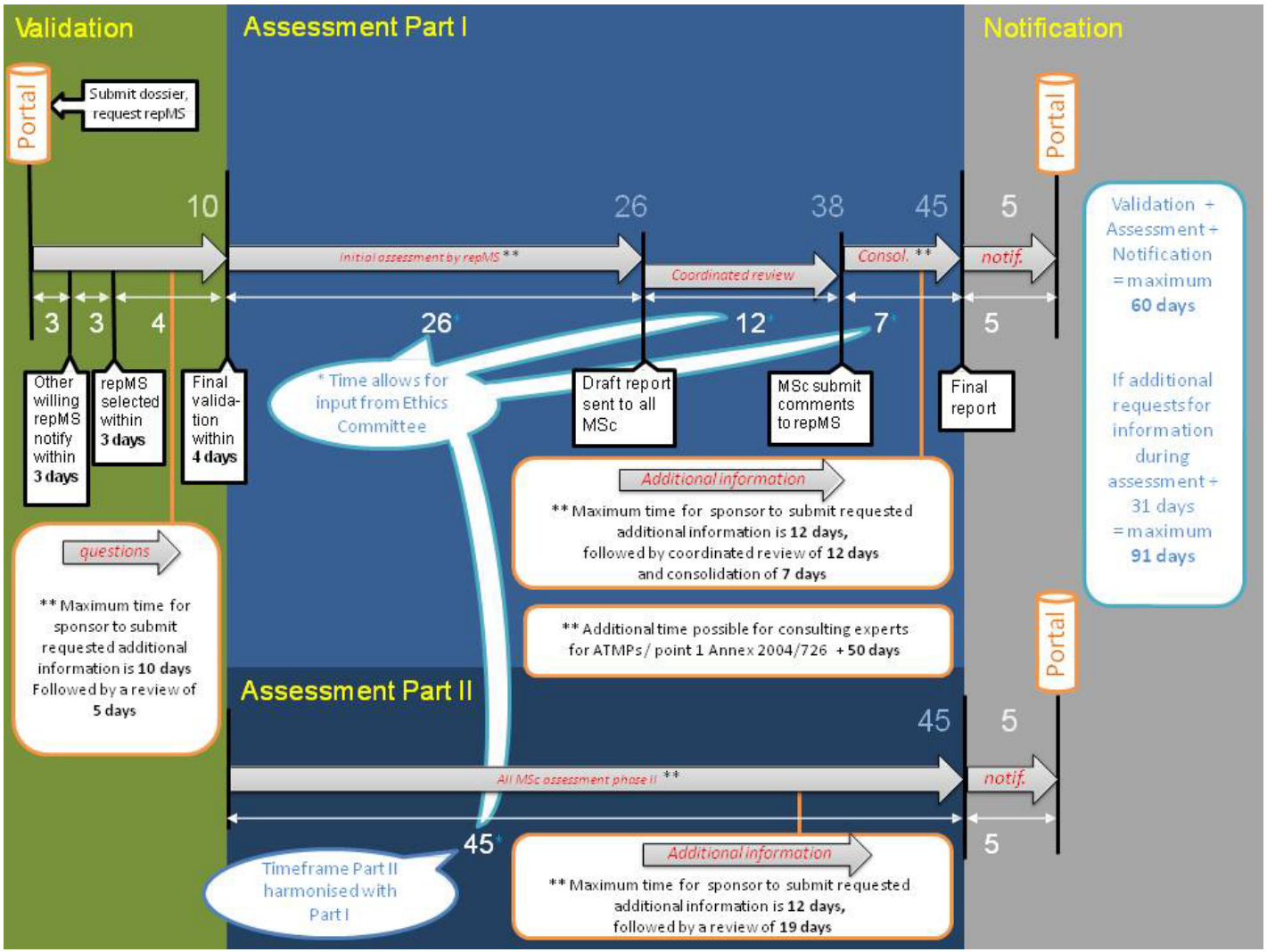
# Article 8 – Decision (2)

- A CMS shall refuse a trial if :
  - it disagrees with the part I decision
  - the part II decision is negative
  - An ethics committee has give a negative opinion (as defined nationally) – appeal mechanism to be foreseen
- If the RMS opinion is negative, it is negative for all MSC
- Tacit approval system means automatic approval when the time has lapsed
- Authorisation has an expiry date of 2 years

# Initial trials process : decision

- Each MSC needs to notify its single decision within 5 days of the reporting date or from the last day of the part II decision (whichever is later)

- The date of this decision is the notification date

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# Article 9 – Persons assessing the application

- Member states need to assure that persons validating and assessing the applications have no conflict of interest
- Independence of the sponsor, trial site, investigators and persons financing is needs to be guaranteed
- Annual declaration of financial interests
- Assessment to be done by reasonable number of persons who have the qualifications and experience
- At least one lay person

«non addetti ai lavori»

# Article 10 – Specific considerations for vulnerable populations

- General provision : when specific groups or subgroups of subjects participate, specific expertise is required
- Identified categories : minors, incapacitated subject, pregnant/breastfeeding women
- Persons with expertise in the disease and population need to be consulted

# Article 11,12 & 13 – Separate assessment, withdrawal, resubmission

- Sponsor can request to apply for an assessment of part I only
- Within 2 years after the (positive) part I decision, the sponsor can apply for an authorization limited to aspects in part II
- The sponsor can withdraw the application at any time before the reporting date.
- Withdrawal impacts all memberstates concerned and needs to be justified.
- Resubmission after withdrawal or refusal is possible, and is considered to be a new application

# Article 14 – Addition of member states

- Additional member states can be added after the notification date of the initial application. No substantial modifications can be ongoing
- RMS from the initial application remains
- Part I decision of the new MSC should be the RMS's decision except when:
  - Subjects receive inferior treatment compared to the normal clinical practice in that member state
  - Specific rules in national legislation are not met
  - Considerations on safety or reliability exist

- Process similar to part I / II process for initial trials
- New member states can communicate considerations on part I to the RMS and assesses part II

# Addition of a MS: assessment of part I

- D0: submission date (no validation foreseen)
- D+47 : additional member state may communicate considerations to the RMS on part I AR
- RMS can request additional information on Part I from the sponsor between submission date and D+52, timeline is extended with 31 days
- Sponsor submits the additional information within 12 days
- The answer is jointly reviewed by all CMS, considerations are shared within 12 days
- Final consolidation by the RMS within 7 days.

# Addition of a MS: assessment of part II

- D0: submission date (no validation foreseen)
- D+52 : additional MS produces the part II AR
- Additional MS can request additional information on Part II from the sponsor between submission date and D+52, timeline is extended with 31 days
- Sponsor submits the additional information within 12 days
- Final assessment by the additional MS shall be performed within 19 days.
- If the sponsor has not provided a response within the timeline, the application is considered to be lapsed

# Addition of a MS: decision

- An additional MS shall refuse the trial if :
  - it disagrees with the part I decision
  - the part II decision is negative
  - An ethics committee has give a negative opinion (as defined nationally) – appeal mechanism to be foreseen
- Tacit approval system means automatic approval when the time has lapsed

# Challenges (1)

Collaboration mechanisms between member states :

- Importance of coherence in the decision making process
- VHP experience shows collaboration between NCAs can work…
- … but VHP is limited in numbers, is NCA-only, and is coordinated centrally

# Challenges (2)

Definition of roles and responsibilities of NCA and EC :

- NCA + EC in current setting ≠ memberstate
- Shift in operational scope for the concerned organisations
- Important differences in responsibilities linked to the CTR requirements (e.g. independence of the trial site, composition, expertise,…)
- Clarity on the workprocessflow is needed !

# Substantial Modifications

# Overview

- Articles in the Regulation
- Part I modification
- Part II modification
- Part I and II modification

# Articles in the Regulation

Introduction #23

- Clinical trials are usually subject to many modifications after they have been authorised. Those modifications may relate to the conduct, the design, the methodology, the investigational or auxiliary medicinal product, or the investigator or clinical trial site involved. Where those modifications have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial, they should be subject to an authorisation procedure similar to the initial authorisation procedure.

# Articles in the Regulation

- Article 2, Definitions, #13
- 'Substantial modification' means any change to any aspect of the clinical trial which is made after notification of a decision referred to in Articles 8, 14, 19, 20 or 23 and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.

- Chapter III, Articles 15 / 16 / 17 / 18 / 19 / 20 / 21 / 22 / 23 / 24

# Part I modification

# Part I modification - Validation

- Submission is through the portal
- Reporting Member State (rMS) is the same as for initial authorisation
- Concerned MS the same too

- Submitted by sponsor
  - Within 5 days – all cMS give any considerations relevant to the application to the rMS
  - Within 6 days – rMS validates the application
    - That it concerns aspect of part I
    - That the dossier is complete

# rMS decision on validation

- YES – sponsor notified = validation date
- NO
  - sponsor informed and has 10 days to rectify the issues through the portal
    - If does not respond then application has lapsed
  - rMS has further 5 days to complete validation
    - OK = validation date
    - Still not right – application deemed to have lapsed

- If the rMS fails to validate on time it is automatically validated.

# Assessment period

- From Validation date
  - 38 days to complete draft assessment report
    - 19 days for draft report
    - 12 days co-ordinated review
    - 7 days consolidation
- Extra 50 days for an ATMP or to consult with experts
- Extra 31 days to ask sponsor for more information
  - 12 days for sponsor to respond
  - 12 days for co-ordinated review
  - 7 days to consolidate

# Part I conclusion

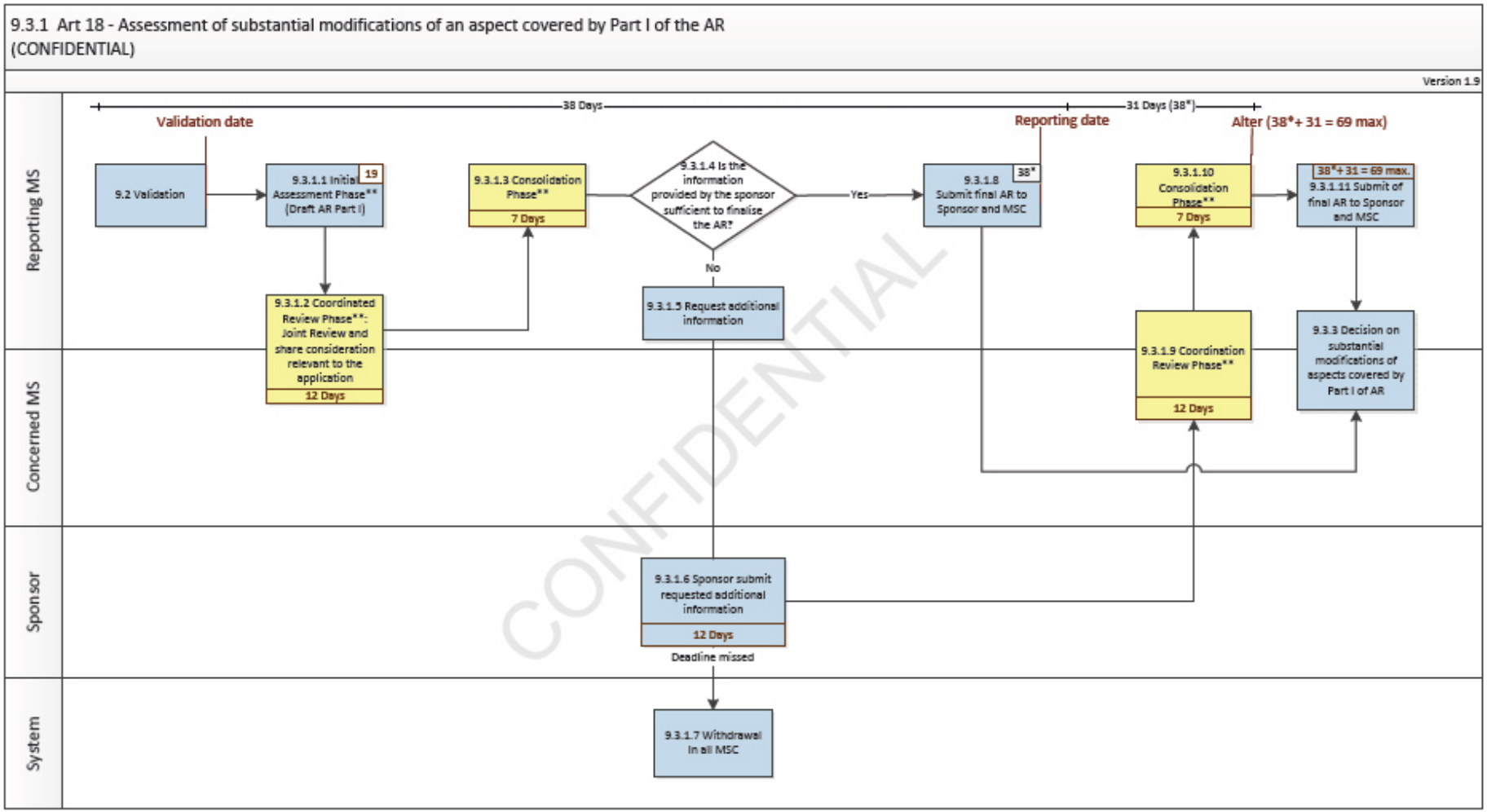
- Each Member State concerned shall notify the sponsor through the EU portal as to whether the substantial modification is
  - Authorised
  - Authorised subject to conditions
  - Authorisation is refused
- Date final report submitted to sponsor and all cMS = reporting date
- Final notification is done by way of a single decision within five days from the reporting date (giving the notification date)

# Part I conclusion

- Where the conclusion of the reporting Member State is that the substantial modification is acceptable or acceptable subject to compliance with specific conditions, that conclusion shall be deemed to be the conclusion of the Member State concerned.
  - a Member State concerned may disagree with that conclusion of the reporting Member State only on the following grounds:
    - when it considers that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned;
    - infringement of its national law as referred to in Article 90;
    - considerations as regards subject safety and data reliability and robustness submitted under paragraph 4 or 6 of Article 18.

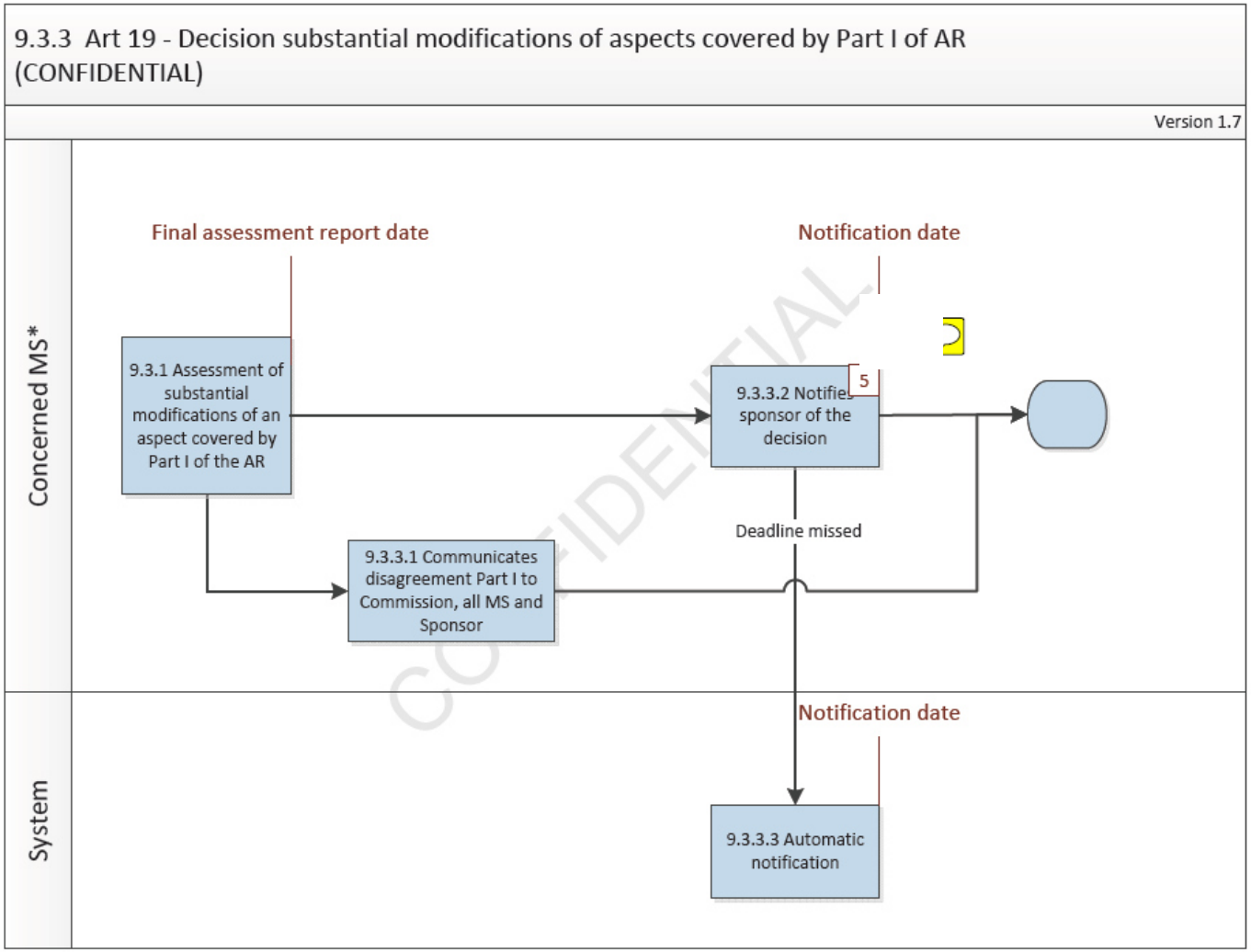
# Part I conclusion

- Where the conclusion of the reporting Member State, as regards the substantial modification of aspects covered by Part I of the assessment report, is that the substantial modification is not acceptable, that conclusion shall be deemed to be the conclusion of all Member States concerned.




*extend the time period for a further 50 days for clinical trials involving an advanced therapy medicinal products or medicinal products as defined in point 1 of the Annex to the Regulation (EC) No 726/2004, for the purpose of consulting with experts

** where, for scientific reasons it is not possible to submit a summary of the results within one year, the assessors have to check that justification is included in the protocol and it is acceptable




*This includes Reporting MS

# Part II modification

- Includes addition of a trial site or change in Principal Investigator

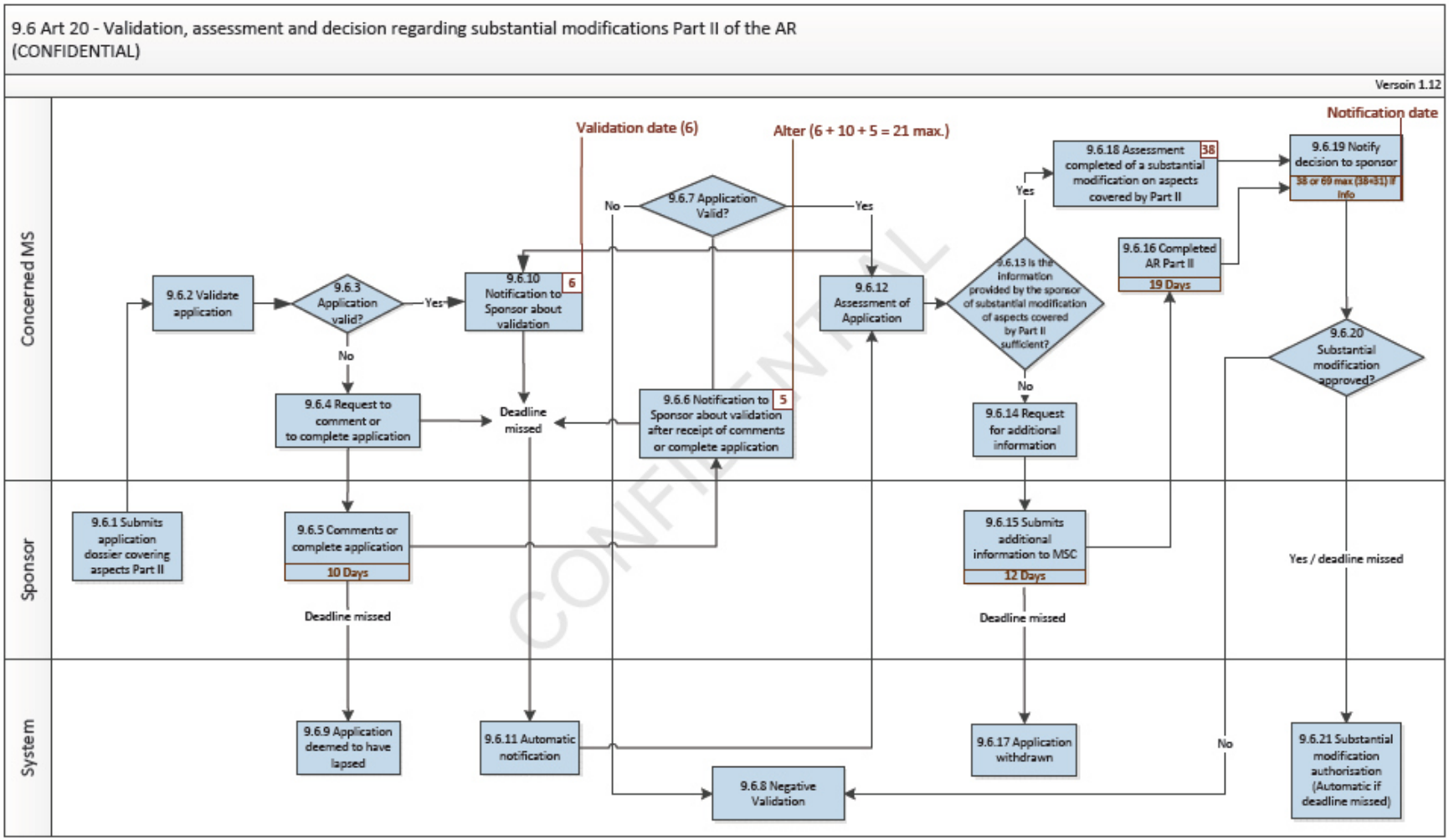
# Validation and assessment

- cMS 6 days to validate
  - Process as per Part I modification

- cMS 38 days to review and complete report
  - Can extend by 31 days if require further information from sponsor

# Part II Conclusion

- The Member State concerned shall assess the application and shall submit to the sponsor, through the EU portal, Part II of the assessment report, including its conclusion, and the decision as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused.

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# Parts I and II modification

# Validation and assessment

- Validated as per Article 17 (Part I modification)
- Aspects of Part I assessed as per Article 18
- Aspects of Part II assessed as per Article 22 (similar to Article 20)

# Conclusion for Parts I and II

- rMS makes conclusion for Part I
  - Authorised / authorised subject to conditions
    - This is deemed the conclusion of that MS only
    - cMS can disagree based on national grounds, as per Article 19(2)
  - If not acceptable – this is the conclusion of that MS only
- If part I is acceptable to a cMS then each cMS also submits its conclusions for Part II
  - Part II can be accepted or refused (as per Article 20(7))

# Article 81 - 9 - Updates

- The sponsor shall permanently update in the EU database information on any changes to the clinical trials which are not substantial modifications but are relevant for the supervision of the clinical trial by the Member States concerned.
- E.g
- Change of applicant
- Change in Sponsor
- Response to a condition – e.g. submission of 3 monthly safety summaries

- Communications of non-substantial modifications which are not relevant for the supervision of the trial by the MS should not be provided.

# Submission of Notification

# Start, end, temporary halt, and early termination of a clinical trial

- Start of trial
  - Within 15 days of start, for each MS
- First visit of first patient
  - Within 15 days of FPFV, for each MS
- End of recruitment
  - Within 15 days, for each MS
  - If restarts – report as per start of trial
- End of trial
  - Within 15 days, for each MS
  - Also notify each MS for EOT in all MS and again for global EOT

# Start, end, temporary halt, and early termination of a clinical trial

- Within 1 year of EOT in all MS
  - Submit summary of results (Annex IV) including lay version (Annex V)
  - Possibility of delaying this with prior approval via the protocol
- If trial was part of an MAA
  - Submit full study report within 30 days of MA being granted, procedure completed or MAA withdrawn
- Temporary halt for reasons not affecting the benefit-risk balance
  - Within 15 days of halt
  - Inform database when resumed
  - EOT if not resumed within 2 years or sponsor decides not to restart
- Early termination for reasons not affecting the benefit-risk balance
  - Date is deemed EOT date

# Start, end, temporary halt, and early termination of a clinical trial

- Temporary halt or early termination by the sponsor for reasons of subject safety
  - Notification within 15 days
  - Include reasons and specify follow-up measures
  - The restart of the clinical trial following a temporary halt shall be deemed to be a substantial modification

# Content of an Application

# E-Application dossier (chapter IV, annex I)

- The application dossier for the authorisation of a CT shall contain all required documentation and information relating to:

  a) the conduct of the CT, including scientific context and arrangements taken,

  b) the sponsor, investigators, potential subjects, subjects and clinical trial sites,

  c) the IMP, and when necessary the AMP, in particular their properties, labelling, manufacturing and control,

  d) measures to protect patients,

  e) justification of the low-intervention character when claimed by the sponsor,

# Application dossier

- Non clinical information shall be based in studies complying with the Union law on the principles of good laboratory practice.

- Clinical data shall have been generated from a CT conducted in accordance with the CT Regulation or Directive, or if conducted outside the EU, in accordance with principles equivalent to those in the EU legislation.

- CT source of the data shall have been registered prior to its start in a public register which is a primary or partner registry or a data provider of WHO ICTRP, or if the results of that CT have been published in an independent peer reviewed scientific publication.

Part I (EU)

Part II (MS)

One CT dossier

Cover letter
EU application form
Protocol
Investigator's Brochure
IMPD
GMP compliance
AMP Dossier
Scientific advice/PIP
Labelling

Recruitment arrangements
Subject info/informed consent
Suitability of investigator
Suitability of facilities
Proof of insurance
Financial /other arrangements
Proof of payment of fee
EU Law on Data protection

EU Portal

# Cover letter

- It shall draw attention to any features which are particular to the CT and need to be paid attention.

# EU CT application form

- It shall include structured information in relation to the sponsor, the main characteristics of the CT, the medicinal products to be used in the CT and MS specific information, including principal investigators and participating sites.

# Protocol

- It shall describe the objective, design, methodology, statistical considerations and organization of the clinical trial.
- This will include among other things:
- a discussion of the relevance of the CT,
- selection criteria, including criteria for withdrawing individual subjects from treatment or from the CT,
- objectives and end-points,
- a description of the expected duration of subject participation and a description of the sequence and duration of all clinical trial periods, including follow-up, if relevant,

# Protocol

- a description of treatments of the CT,
- a description of the publication policy,
- the safety plan, including safety recording and reporting etc.
- With regard to the notification of adverse events (AE), the protocol shall identify the categories of:

  (a) AE or laboratory anomalies that are critical to safety evaluations and must be reported by the investigator to the sponsor, and

  (b) serious AE which do not require immediate reporting by the investigator to the sponsor.

# Protocol

- The protocol shall describe the procedures for:

  (a) eliciting and recording AE by the investigator, and the reporting to the sponsor;

  (b) reporting by the investigator to the sponsor of serious AE which have been identified in the protocol as not requiring immediate reporting;

  (c) reporting of SUSAR by the sponsor to the Eudravigilance database;

  (d) follow-up of subjects after adverse reactions.

# Protocol

- It shall also describe the following information relevant for part II assessment:
- a description of the arrangements to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial subjects, where applicable, unless contained in a separate document;

# Investigator's Brochure (IB)

- The purpose of the IB is to provide the investigators and others involved in the CT with information to facilitate their understanding of the key features of the protocol and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial.

- IB shall be prepared from all available information and evidence that supports the rationale for the proposed clinical trial and the safe use of the investigational medicinal product in the clinical trial and be presented in the form of summaries.

# Investigator's Brochure (IB)

- In case the IMP is authorised  the SmPC shall be the IB.
- If the conditions of use in the CT differ from those authorised, the SmPC shall be supplemented with a summary of non clinical and clinical data that support the use of the IMP in the CT.
- For multinational CT where the MP to be used in each MS concerned is authorised at national level, in case the product is identified by active substance, the sponsor shall choose one SmPC representative of each active substance for the whole CT. Alternatively, in case the IMP is identified by an ATC code, the sponsor may provide a collated document containing information equivalent to that in the representative SmPC for each active substance pertaining to the ATC group.

# Investigator's Brochure (IB): Reference safety information

- If the IB is not the SmPC, it shall contain a clearly identifiable section named 'Reference safety information'.

  The RSI shall contain product information on the investigational medicinal product and on how to determine what adverse reactions are to be considered as expected adverse reactions, and on the frequency and nature of those adverse reactions.

- If the IB is the SmPC, the reference safety information is normally section 4.8 of that SmPC.
- It will serve to assess the expectedness of an adverse reaction.

# Documentation relating to compliance with Good Manufacturing Practice (GMP)

- No documents needed if the IMP is authorised and not modified.
- A copy of the manufacturing authorisation referred to in article 61, in all other cases.
- Certification of the qualified person in the Union that the manufacturing complies with GMP at least equivalent to the GMP in the Union, if the product has not a marketing authorisation in the Union nor in an ICH country and is not manufactured in the Union.
- Documentation to demonstrate compliance with national requirements for processes related to IMP set out in article 61(5).

# Investigational Medicinal Product Dossier (IMPD)

- The IMPD is necessary for an IMP which is not authorised or which being authorised is modified for the purpose of the CT.
- Quality data: the manufacture and control of any IMP (Module 3 of ICH Common Technical document format).
- Non clinical pharmacology and toxicology data: if not provided in the IB.
- Clinical data from previous clinical trials and human experience, if not provided in the IB.
- Overall risk and benefit assessment

# IMPD in cases of Placebo

- Limited to Quality data
- Only necessary in cases where the placebo has different composition than the tested IMP (without considering the active substance) or it is manufactured by another manufacturer or it is sterile.

# Auxiliary medicinal product (AMP) dossier

- No data necessary if the AMP is authorised in the MS concerned.
- In case the product is authorised in other EU country, only the approved SmPC or, when applicable, the SmPC plus non clinical and clinical data that support the use in the clinical trial are needed.
- If the AMP is authorised and not modified, no GMP compliance documents are needed.
- In other cases, documents related to GMP compliance and a dossier similar to IMPD are necessary.

# Scientific advice and paediatric investigation plan (PIP)

- If applicable, a copy of the summary of the scientific advice of the Agency, Member State or third country, with regard to the CT.

- If the CT is part of an agreed PIP, a copy of the Agency's decision on the PIP, and the opinion of the Paediatric Committee, or a link to these documents.

# Labelling

- A description of the content of the labelling of IMP (and AMP?) to show compliance with annex VI.

# Application dossier (MSC specific info)

1. Recruitment arrangements.
2. Subject information, informed consent form and informed consent procedure.
3. Suitability of the investigator.
4. Suitability of the facilities.
5. Proof of insurance cover or indemnification
6. Financial and other arrangements (specially transactions and compensations paid to subjects and investigators/site).
7. Proof of payment of fee.
8. Proof that data will be processed in compliance with Union Law on data protection.

# E-Application dossier SM (Annex II)

- The application dossier for the authorisation of a substantial modification (SM) shall contain all required documentation and information relating to:
  - a) identification of the CT which are substantially modified,
  - b) a clear description of the SM and the reasons for it (all changes tabled: previous and new wording and reason),
  - c) data and information in support of it, where necessary,
  - d) a clear description of the consequences of the SM as regards, the rights and safety of the subject and reliability and robustness of the data generated in the CT,
  - e) a new version of the updated document if too many changes,
  - f) an update of the EU application form.

# Need for traceability of changes

- Every document should have a version date and document type.
- Product specific documents (IMPD and IB) should be related to the specific MP.
- The sponsor may refer to any previous applications, providing only new data.
- It would be important to know if certain changes have already been approved in other CT (either in the initial CTA or by a SM).

**Protocol 1**
**IMPD X1**

**SM Protocol 1**
**IMPD X2**

**Protocol 3**
**IMPD X3**

**Protocol 2**
**IMPD X2**

**SM Protocol 2**
**IMPD X3**

# Transparency requirements

- The CT dossier will be stored in the EU database.
- Rules to make public the information in the EU CT database are set in:
- Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/10/WC500195084.pdf

# Safety

# CHAPTER VII Safety Reporting

- Article 40 – Electronic database for safety reporting (EMA)
- Article 41 – Reporting of AEs, SAEs by the investigator
- Article 42 – Reporting of SUSARs from sponsor to the Agency
- Article 43 – Annual reporting by the sponsor to the Agency
- Article 44 – Assessment by Member States*
- Article 45 – Technical aspects (refers to annex III)*
- Article 46 – Reporting with regard to auxiliary medicinal products*

# Safety reporting

- Safety reporting requirements are largely similar to the current requirements within 2001/20/EC, CT-1 and CT-3
- Member states will be obliged to collaborate with safety assessment under the new regulation
- Member states may consult each other in relation to corrective measures
- A pilot worksharing procedure is underway among active CTFG members
- safety training course/workshop are being held through EU NTC to facilitate harmonisation of assessment of safety data across member states

# Annual safety reporting

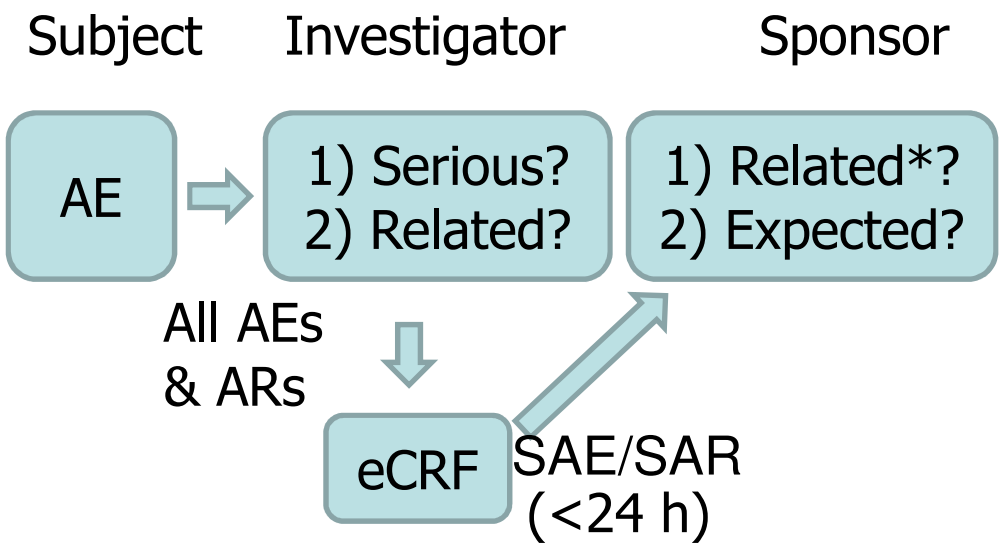
- Progetto pilota molto preliminare
- Identificazione lead MS
- Combinato per IMP?

- Portale e Eudravigilance
- Coordinamento tra MS

# Art. 40-43 summary: CT safety reporting routes

| Subject | Investigator | Sponsor | EMA | MS Concerned |
|---|---|---|---|---|
| AE | | | | |

# Art. 40-43 summary: CT safety reporting routes

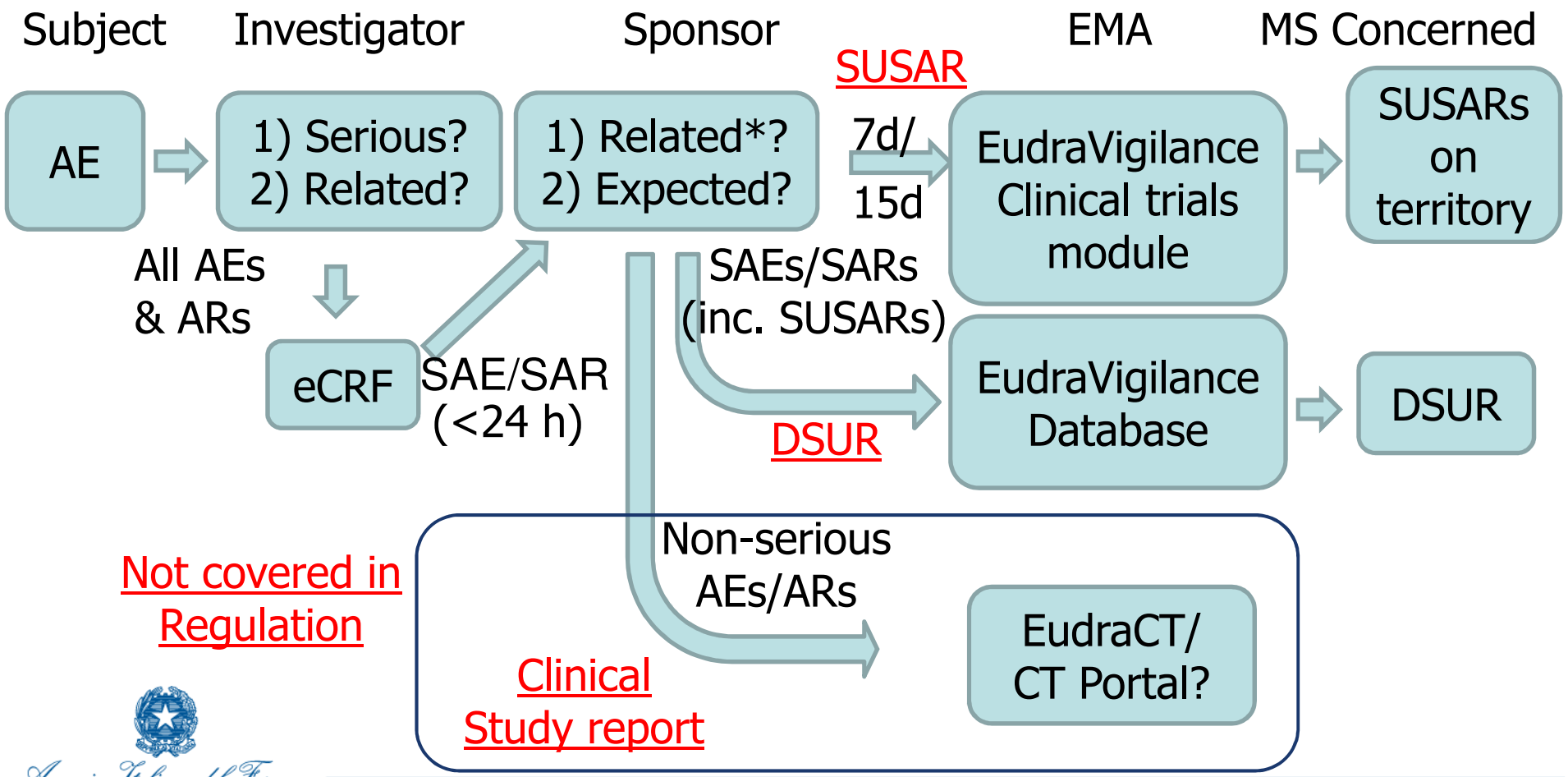



Hospitalisation/prolongs hospitalisation
Fatal, life threatening, persistent disability, congenital abnormality, important event

All AEs & ARs to be recorded & reported unless protocol provides differently

Related? Yes/no
Yes = suspected adverse reaction
No = adverse event

# Art. 40-43 summary: CT safety reporting routes

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# Article 44 – DSUR assessment by MS

- "2. Member states shall cooperate in assessing the information reported in accordance with articles 42 and 43."
- - significant change to current practice
- How will this work?
- No details in the regulation – task for CTFG
- CTFG safety subgroup proposal: A safety member state (saMS) will lead the assessment of clinical trial safety data
- "The Commission may, by means of implementing acts, set up and modify the rules on such cooperation."

# Article 44: worksharing Safety assessment MS

Roles and responsibilities (not defined in reg):

1. Assessment of DSUR, SUSARs other safety issues that may arise over 1 year period (e.g. urgent safety measures, impact of CHMP/PRAC recommendations on trial populations)
2. Prepare DSUR assessment report & draft any queries to sponsor
3. Liaise with other member states concerned (through EMA IT system) regarding proposed queries to sponsor
4. Agree actions among member states concerned
5. Ensure reference safety information is uniform for IMPs and up to date for all trials

# Article 44: worksharing Safety assessment MS

Selection procedure (as currently proposed by CTFG):

3 scenarios:

1. Mononational CT/IMP – Member state is saMS
2. IMP with one multinational CT: RMS will act as saMS
3. IMP with >1 multinational CTs:
   1. All MSCs are invited to volunteer for role of saMS (10 days after DSUR submission)
   2. Day 14: agreement on saMS

# Article 44: worksharing
# CTFG safety subgroup DSUR worksharing pilot

- In preparation for the requirements of article 44 of the new CT regulation, CTFG safety subgroup has initiated a DSUR worksharing pilot
- Member states have been allowed select DSURs of IMPs for assessment
- Assessment report is shared with other member states & on VHP database (safety section)
- No strict timelines enforced at present – focus on learning & harmonisation of assessment procedure

# Article 44: worksharing
# DSUR worksharing pilot – experience to date

- Template assessment report (Jan 2016): 4.5 pages, some "optional" sections

**ASR - ASSESSMENT REPORT**

Procedure number:
Final report ☐

Investigational Medicinal Product name(s):
INN(s)
Trade name(s)
IMP code (s)

| |
|---|
| **1. ADMINISTRATIVE INFORMATION**<br>EU CT number(s): |
| **1.1. Sponsor(s):** |
| Contact or Legal representative, if different from sponsor: |
| **1.2. Investigational Medicinal Product(s)** |
| DIBD/IBD:<br>Therapeutic Indication(s): (MedDRA):<br>EEA Marketing Authorisation granted: Yes ☐ No ☐<br>If yes, used within licensed indication in all trials covered by the ASR: Yes ☐ No ☐<br>Therapeutic class / Mode of action (if known):<br>Further details (if necessary): |
| **1.3. ASR** |
| ASR number<br>Reporting period: |

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# Article 45: Technical details (annex III) Very similar to current CT-3 guidance

- Reference Safety Information – content and timing of updates
- Content:
- 2.2 (6).The expectedness of an adverse reaction shall be set out by the sponsor in the RSI. Expectedness shall be determined on the basis of events previously observed with the active substance and not on the basis of the anticipated pharmacological properties of a medicinal product or events related to the subject's disease.
- No further detail

# Annex III Safety Reporting (details)

1. Reporting of SAEs by the investigator to the sponsor
2. Reporting of SUSARs by the sponsor to the agency
3. Annual Safety Reporting by the Sponsor*

# Chapter VIII - Conduct & supervision

Article 48 – Monitoring

Article 52 – Reporting of serious breaches

Article 53 – Other reporting obligations relevant for subject safety

Article 54 – Urgent safety measures

Article 59 – Auxiliary medicinal products

# Chapter XIII – Corrective measures

Article 77 – Corrective measures to be taken by Member states

# Annex III Safety Reporting (details)

- SUSAR 2017: Eudravigilance
- SUSAR 2018: Eudravigilance
- SUSAR 2019: Eudravigilance!

- Regole per il reporting da sperimentatore a sponsor
- Annual safety reporting:

CT birth date

Cooperazione tra MS

Upload e gestione tramite UE portal

# Annex III - Expectedness
# Reference safety information – content (Q&A)

- The content of the Reference Safety Information should include a list of observed adverse reactions which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in previous clinical trials and/or on a thorough evaluation of causality from individual case reports.

- This list should include expected adverse reactions to the IMP and should describe the nature of the listed reactions, the expected severity and frequency.

# Annex III - Expectedness
# Reference safety information – content (Q&A)

- The listed adverse reactions should be based on reactions previously observed and not on the basis of what might be anticipated from the pharmacological properties of a medicinal product (see section 2.C of the note for guidance ICH E2A).

- An expectedness assessment is required for expedited reporting of SUSARs from sponsors to agencies *and for the identification of SUSARs in the cumulative summary tabulation of serious adverse reactions in the annual safety report (DSUR).*

# Updating Reference Safety Information
# Current CTFG guidance

- Any change to an RSI is considered a substantial amendment and it requires to be justified with supportive data.
- It is recommended to update the RSI, if necessary, in alignment with the annual period for a development safety update report (DSUR).
- If the date of RSI update is aligned this way the DSUR can act in part as justification for the RSI changes.
- In case your RSI is updated prior to the end of the reporting period of the DSUR a detailed justification by data is expected.

# Article 46:
# Reporting with regard to AMPs

- Safety reporting with regard to auxiliary medicinal products shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC.

- - All observed suspected adverse reactions within the EU should be reported to EudraVigilance database as spontaneous ARs (for AMPs with marketing authorisation)

- - All Serious adverse events in all trials covered by the DSUR should be included in the DSUR of the IMP as per ICH E2F and EMA DSUR guidance

# Chapter VIII: Conduct, supervision, training & experience, auxiliary MPs

- Article 48: Monitoring:
- The extent an nature of monitoring shall be determined by the sponsor on the basis of an assessment that takes into consideration all characteristics of the clinical trial, including the following characteristics:
- a) Whether the trial is a low-intervention trial*
- - Implications for safety reporting requirements
- b) The objective and methodology of the clinical trial; and
- c) The degree of deviation of the intervention from normal clinical practice

# Chapter VIII: Conduct, supervision, training & experience, auxiliary MPs

- Article 52 - Reporting of serious breaches
- 1.The sponsor shall notify the Member States concerned about a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach through the EU portal without undue delay but not later than seven days of becoming aware of that breach.
- 2.For the purposes of this Article, a 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

# Chapter VIII:
# Article 53 - Other reporting obligations

- 1.The sponsor shall notify the Member States concerned through the EU portal of all unexpected events which affect the benefit-risk balance of the clinical trial (but are not SUSARs) no later than 15 days from the date the sponsor became aware of this event.

- 2.The sponsor shall submit to the Member States concerned, through the EU portal, all inspection reports of third country authorities concerning the clinical trial.

# Chapter VIII:
# Article 54 – Urgent safety measures

- 1.Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects.

- 2.The sponsor shall notify the Member States concerned, through the EU portal, of the event and the measures taken. That notification shall be made without undue delay but no later than seven days from the date the measures have been taken.

# Chapter VIII:
# Article 59 – Auxiliary medicinal products

1. Only authorised auxiliary medicinal products may be used in a clinical trial.
2. Paragraph 1 shall not apply where no authorised auxiliary medicinal product is available in the Union or where the sponsor cannot reasonably be expected to use an authorised auxiliary medicinal product. A justification to this effect shall be included in the protocol.

- Safety reporting requirements for of unauthorised AMPs will be addressed in the Q&A

# Chapter XIII Supervision by member states
# Article 77 – Corrective measures

- 1.Where a Member State concerned has justified grounds for considering that the requirements set out in this Regulation are no longer met, it may take the following measures on its territory:

  (a) revoke the authorisation of a clinical trial;

  (b) suspend a clinical trial;

  (c) require the sponsor to modify any aspect of the clinical trial.

# Chapter XIII Supervision by member states Article 77 – Corrective measures

- 2.Before the Member State concerned takes any of the measures referred to in paragraph 1 it shall, except where immediate action is required, ask the sponsor and/or the investigator for their opinion. That opinion shall be delivered within seven days.

- 3.The Member State concerned shall immediately after taking a measure referred to in paragraph 1 inform all Member States concerned through the EU portal.

- 4.Each Member State concerned may consult the other Member States concerned before taking any of the measures referred to in paragraph 1.

# GCP Considerations

# Article 47 Compliance with the Protocol and GCP

- The Sponsor and Investigator are responsible for ensuring that the protocol is followed and that the principles of GCP are adhered to

- ICH GCP is referred to in the Regulation and the sponsor and Investigator *'shall take appropriate account of the quality standards and the ICH Guidelines on GCP'*

- Recital 43 also states these guidelines *'should be taken appropriately into account'*

This does not make ICH GCP a legal requirement

# Article 48 Monitoring

- The Sponsor is required to 'adequately' monitor the trial – this is to ensure that:
  - The safety and the well-being of subjects are protected
  - The data is reliable and robust
  - The Regulation is being followed

  The Regulation allows for a proportionate approach to be taken with regards to monitoring – taking into consideration whether the trial is low interventional, the methodology and the deviation form normal clinical practice

# Article 48 Monitoring (continued)

- In practice, monitoring/oversight can be performed by a number of different methods:
- Onsite monitoring
- Central monitoring
- Statistical monitoring
- Oversight Committees such as Independent Data Monitoring Committees or Trial Steering Committees
- The Regulation therefore allows the use of a number of different methodologies depending on the characteristics of the trial

# Article 48 Monitoring (continued)

- Commission Guidance on risk proportionate approaches in clinical trials within the scope of the Regulation currently in draft – this includes approaches to monitoring

- An assessment must be conducted to determine the type and levels of monitoring required;

- for example the assessment may determine that no onsite monitoring is required and remote monitoring is sufficient

# Article 48 Monitoring (continued)

- The risk assessment can identify potential risks; the monitoring strategy may be able to mitigate some of those risks, for example if consent in vulnerable populations is a risk area, on-site monitoring may be required to ensure that the appropriate consent procedures are followed

- The Monitoring plan and assessment should be reviewed regularly and as new information comes to light

# Article 49 Suitability of individuals involved in conducting the clinical trial

- Investigator – must be a medical doctor – or a person following a profession which is recognised in the MS concerned as qualifying for an investigator (scientific knowledge/experience in patient care) – may vary between MS
- Other individuals – suitably qualified by education, training and experience to perform their tasks
- In practical terms this needs to be demonstrated by documented training in for example GCP, relevant SOPs, an up to date CV, job description etc.
- Any tasks delegated by the investigator to his/her staff must be authorised

# Article 56 Recording, Processing, handling and Storage of Information

- The principle of managing data to ensure that it can be verified and is accurately reported – key principle of GCP
- Same wording as Article 5 of 2005/28; however 'processed' is also included in the Regulation
- Personal data must also be protected
- There is also a requirement to ensure that technical and organisational measures are implemented to protect clinical trial information and personal data against unlawful access, disclosure, destruction etc. This is particularly important with the use of networks to transmit data and technology (such as cloud) to store information

# Article 57 Trial Master File

- Clinical Trials Master File shall at all times contain the essential documents relating to that clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated taking account of all the characteristics of the CT, including whether the CT is a low-interventional CT.

- It shall be readily available and directly accessible upon request to the MS

# Article 57 Trial Master File (cont)

- The Trial Master File should allow full reconstruction of the trial, via the essential documents and it is also the basis for inspection

- The content of the TMF is often misunderstood – more than section 8 of ICH GCP

- The TMF should be viewed as a set of documentation and/or computer systems content that together confirm the validity of the trial conduct and the integrity of data collected without additional explanation from the associated sponsor or site staff

# Article 57 Trial Master File (cont)

- EMA Guidance on the TMF is currently in draft
- The Regulation does not differentiate between paper and electronic documents, therefore direct access also applies to electronic systems as well as paper
- Management of TMFs can be quite complex for large, global trials and also with the involvement of CROs and vendors
- There should be a record of the locations of all the documentation that is considered to be part of the TMF – this could include a number of different locations and systems

# Organisation of the Trial Master File


# Article 58 Archiving

- Clinical Trials Master File must be archived for 25 years
- Must be archived in such a way that it is readily available and accessible to the competent authorities – the media used must ensure that the contents remain legible and complete for the 25 years
- Transfer of ownership must be documented (mergers, closure)
- Sponsor must appoint a named archivist
- Any alternation to the TMF must be traceable (audit trail)

# Article 78 – Member State Inspections

- Inspectors must be appointed – qualifications and training are covered in the Implementing Act
- Planned Inspections (in EU and third countries) are entered onto the EU database – therefore all MS are aware of upcoming inspections
- For inspection conducted in relation to a MAA, the EMA will coordinate cooperation between member states
- Inspection reports will be submitted to the database (and will becomes public)

# Chapter V: Protection of subjects and informed consent

# Article 28: General rules

- Benefits justify risks and inconveniences
- Informed consent is given (subject or legal representative)
- Rights of subjects are safeguarded
- Trial designed to minimise pain, fear and risk to subjects
- Medical care provided is responsibility of an appropriately qualified medical doctor/dentist
- Subjects provided with contact details for information
- No 'undue influence' (eg financial) to participate

# Article 28: General rules

- Subject (or legal rep) can give consent for use of data outside the protocol of the clinical trial exclusively for scientific purposes.

- Subject (or legal rep) can withdraw consent at any time (doesn't affect activities already carried out)

# Article 29: Informed consent

- (a) Information given will enable subject to understand

(i) the nature, objectives, benefits, implications, risks and inconveniences of the clinical trial;

(ii) the subject's rights and guarantees

(iii) the conditions under which the clinical trial is to be conducted, including the expected duration of participation

(iv) the possible treatment alternatives, including the follow-up measures if the participation of the subject in the clinical trial is discontinued;

# Article 29: Informed consent

- (b) kept comprehensive, concise, clear, relevant, and understandable to a layperson;
- (c) provided in a prior interview with a member of the investigating team who is 'appropriately qualified'
- (d) include information about the applicable damage compensation system referred to in Article 76(1)
- (e) include the EU trial number and information about the availability of the clinical trial results.

# Article 29: Informed consent

- Form is signed and dated by interviewer and subject (or legal rep). If cant write – recorded by other means but witnessed.
- Interviewer to verify subject (legal rep) has understood
- Adequate time given to consider decisions
- National provisions for who needs to sign and assent by minors

# Article 30: Informed consent in cluster trials

- For mono-national trials. National law can allow simplified informed consent
- Still need (a), (b), (d), (e) of Article 29 (ie interview not needed)
- Conditions:
  - Groups of subjects rather than individual subjects randomised
  - L.I.T. and IMPs are used in as per MA
  - No other interventions
  - Protocol justifies reasons for simplified consent

# Article 31 & 32: Clinical trials on incapacitated subjects and minors

- Consent of legal rep obtained
- Subject has been given information in line with their capacity to understand
- If the subject wants to withdraw this is respected
- No incentives/inducements to participate
- Trial is essential for these subjects and relates to a condition suffered by the subjects
- Expectation of benefit
- Shall take part in IC as far as possible

# Article 32: Clinical trials on minors (specifics)

- If during a clinical trial the minor reaches the age of legal competence to give informed consent as defined in the law of the Member State concerned, his or her express informed consent shall be obtained before that subject can continue to participate in the clinical trial.

# Article 33: Clinical trials on pregnant or breastfeeding women

- Potential for direct benefit for woman, embryo, foetus or child.
- If no direct benefit then need to ensure:
  - Comparable trial cannot be carried out in a different population
  - Trial may benefit other pregnant/breastfeeding women, embryos, foetuses or children
  - Trial poses minimal risk and burden
- Particular care taken not to adversely impact health of child in trials in breastfeeding women
- No incentives/inducements to take part

# Article 34: Additional national measures

- Member States may maintain additional measures regarding persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision, cannot take part in clinical trials, or persons in residential care institutions.

# Emergency trial


Article 35: Clinical trials in emergency

- Consent given after decision to include subject in the trial (as per the protocol)
- Urgent, life-threatening or sudden serious condition
- Expectation of direct clinical benefit (trial relates to that condition)
- Timing means impossible to give prior info or get IC
- Investigator certifies that they are not aware of any subject objections (expressed previously)
- Trial poses minimal risk and burden

# Emergency trial


Article 35: Clinical trials in emergency

- After intervention – provide information and obtain IC to continue in trial from subject or legal rep.
- If consent is from legal representative – consent to continue is obtained from subject as soon as he or she is capable
- If subject (or legal rep) does not give consent he or she shall be informed of the right to object to the use of data obtained from the clinical trial.

# Low interventional trial


*Article 5*

Submission of an application

"The sponsor shall, when applying for a low-intervention clinical trial, where the investigational medicinal product is not used in accordance with the terms of the marketing authorisation but the use of that product is evidence-based and supported by published scientific evidence on the safety and efficacy of that product, propose one of the Member States concerned where the use is evidence-based, as reporting Member State."

# Clinical Trials Manufacturing, Importation and Labelling aspects

Agenzia Italiana del Farmaco
AIFA

# Items to be covered

- Overview of the requirements of CT regulation with respect to Investigational Medicinal Products (IMPs) and Auxiliary Medicinal Products (AMPs)
  - Chapter IX
  - Article 61 – Authorisation for Manufacture and Import
  - Article 62 – Responsibilities of the Qualified Person (QP)
  - Article 63 – Manufacturing and Import
  - Article 64 – Modifications of authorised IMPs
  - Article 65 – Manufacturing of AMPs
  - Chapter X labelling requirements
- Highlight key changes and potential challenges for Regulatory Agencies

# Article 61 – Authorisation for Manufacture and Import

- Manufacturer's authorisation (MIA(IMP)) required for manufacturing and importation of IMPs
  - Suitable and sufficient premises, technical equipment and controls required
  - Should have the services of at least one QP permanently and continuously at its disposal
  - Should specify the types and pharmaceutical forms of IMP, and manufacturing/importation sites

- These are all existing requirements under Directive 2001/20/EC and so no impact on the existing systems in place for MIA(IMP) licence application systems is expected

# Article 61 – Authorisation for Manufacture and Import

- Article 9(2) of 2005/28/EC provided an exemption. MIA(IMP) not required for reconstitution prior to use or packaging in hospital, health centres or clinical …..used in those institutions
- Article 61(5) also includes an exemption. MIA(IMP) not required for:
  - Re-labelling or re-packaging…carried out in health centres and clinics…by pharmacists or other persons legally authorised….used in hospitals, health centre or clinics taking part in same clinical trial in same Member State
  - Preparation of diagnostic radio pharmaceuticals
  - Preparation of prescriptions for individual patients
  - Processes subject to appropriate and proportionate requirements to ensure subject safety, and reliability and robustness of data
  - Member States shall conduct regular inspections

# Article 61(5) – Changes and Challenges

- Expanded scope of exemption – do Member States have knowledge and expertise to inspect these areas?
- GMP/GCP interface – who will perform the inspections?
- Standards expected – what does 'appropriate and proportionate requirements mean?
- Frequency – how often is 'regular'
- Harmonisation of approach – need for visibility of how each Member State plans to implement national legislation for exempted activities

# Article 62 – Responsibilities of the Qualified Person

- QP required to certify each batch of IMP complies with GMP as set out in Article 63
- Under Directive 2001/20/EC and Annex 13, QP is also required to ensure compliance with the product specification file and registered details of CTA
- No change is scope of QP role intended
- Reference to need for QP to check and confirm compliance with GMP and information pursuant to Article 25 of EU Regulation No. 536/2014 included in Commission Delegated Act GMP for IMP

# Article 63 – Manufacturing and Import

- IMPs shall be manufactured to GMP, apart from the exempt processes identified in Article 61(5)
- The Commission shall adopt delegated acts to specify the principles and guidelines of GMP and arrangements for inspection
  - Initial public consultation on Delegated Act GMP for IMP closed in November 2015
- Imported IMPs subject to equivalent GMP
- Member states to ensure compliance with Article 63 by means of inspection

# Article 63 – Changes and Challenges

- No change in expected GMP standards for IMPs that are not covered by the Article 61(5) exemption
- No change in expected GMP standards for imported IMPs – QP declaration of equivalent GMP still required
- Some concern over intent of Delegated Act GMP for IMP requirement for inspection of third country manufacturers
  - Based on assessment of risk – but is no inspection acceptable?
  - May have inspection resource implications for Member States?
  - May have timeline implications for clinical trial approvals?

# Article 64 – Modifications of authorised IMPs

- Articles 61, 62, 63 apply to modifications to authorised IMPs
- If you have a commercial 'off the shelf' product that is being modified for use in the trial, the modification activities
  - Need to be performed by a site holding an MIA(IMP)
  - Need to performed according to GMP
  - Need to be QP certified

- These are all existing requirements under Directive 2001/20/EC

# Article 65 – Manufacturing of AMPs

- AMPs are medicines required for the trial but are not IMPs
- Commonly know as NIMPs under Directive 2001/20/EC
- Manufacture needs to be subject to equivalent GMP as set out in Article 63(1)
- If the AMP is a commercial 'off the shelf' product that is being modified for use in the trial, the modification activities needs to be subject to equivalent GMP as set out in Article 63(1)
- Need to be manufactured to equivalent GMP but
  - Do not need to be performed by a site holding a MIA(IMP)
  - Do not need to be QP certified

# Article 65 – Changes and Challenges

- Definition of AMP – some confusion?
  - Clinical Trials Manufacturing, Importation and Labelling aspects
  - Challenge agents, rescue medication, but are concomitant medications included?
  - Guidance needed in updated Eudralex Vol 10

# Article 65 – Changes and Challenges

- Change to standards of GMP?
  - Equivalent standard of GMP now expected
  - Previous expectation in Eudralex Vol 10, Note to Applicants was for 'appropriate GMP requirements foreseen for the safety of the patients should still be applied and the sponsor should ensure that NIMPs are of appropriate quality for the purposes of the trial'
  - Is equivalent standard of GMP already being applied?
- Who is responsible for checking equivalent GMP standards have been applied?
  - No reference to Member states ensuring compliance with Article 63 by means of inspection as in Article 61 and 63
  - Sponsor responsible for quality of AMPs?

# Chapter X labelling requirements

- A list of information which is to appear on the outer packaging and immediate packaging for different products (authorised IMPs/AMPs, unauthorised IMPs/AMPs, radiopharmaceuticals) is provided in Annex VI of EU Regulation No. 536/2014

- The language of the information on the label is determined by the Member State concerned and the product may be labelled in several languages

# Chapter X – Changes and Challenges

- Annex VI requirements are considered by some Member States as being less flexible than current EU GMP Annex 13 requirements
  - Not all Member States have national requirements for period of use/expiry dates

- Annex VI (D) replacing of information allows for some particulars to be omitted from the label of a product and made available by other means e.g. central information or interactive response technology systems

# Chapter X – Changes and Challenges

- Particulars that cannot be omitted include period of use information on both the immediate and the outer packaging
  - EFPIA have lobbied Commission
  - Concerned about restrictions on use of electronic systems
  - Concerned about risk of mix up in opening packaging to update primary containers

- Potential for Annex VI to be updated once EU Regulation No. 536/2014 becomes effective

# Summary & Impact on MS

# Regolamento (UE) 536/2014

## Base legale

- Pubblicato il 27 maggio 2014
- Applicazione a decorrere da sei mesi dopo la conferma pubblicata in G.U. dell' UE, della piena funzionalità del portale e banca dati UE
- Sono previste disposizioni transitorie

D.L. 24 giugno 2003, n. 211
Direttiva 2001/20/CE

Regolamento (UE) n. 536/2014

# Regolamento (UE) 536/2014

## Base legale

- Previsti Atti Delegati della Commissione UE su:
  - Aggiornamento degli Annexes del Regolamento
  - Principi e Linee Guida GMP (Dir 2003/94/CE, Annex XIII)
  - Dettagli su Ispezioni GCP e qualification/training degli Ispettori (Dir 2005/28/CE)
  - Inoltre:
    - Revisione LG già esistenti CT-1 e CT-3
    - Preparazione di un nuovo documento di Q&A

# Regolamento (UE) 536/2014

## Background

- Necessità di assicurare la produzione di dati affidabili e robusti, di alto livello scientifico, garantendo i diritti e la sicurezza del paziente
- Verso una trasparenza sempre maggiore sui risultati dei trials clinici
- Ridotti al minimo gli ambiti di autonomia normativa a livello nazionale

# Regolamento (UE) 536/2014

## Background

- Necessità di rendere competitiva l'UE nella ricerca clinica
  - Diminuzione di CTAs tra il 2007 e il 2011
  - Aumento dei costi di conduzione
  - Incremento tempo medio di attesa per avviare una SC
  - Direttiva recepita con diversi requisiti nei diversi stati membri
  - I costi assicurativi sono aumentati

*Source: Concept Paper elaborato dalla Commissione Europea 2011*

# Regolamento (UE) 536/2014

## Impatto

- Non una Direttiva ma un Regolamento: maggiore armonizzazione fra gli Stati Membri (SM)
- Armonizzazione: il portale permetterà di effettuare una singola domanda di autorizzazione per sperimentazione clinica ad Autorità Competente (AC) e Comitato Etico (CE), e anche ai fini di registrazione pubblica (registro primario per sperimentazioni cliniche)
- Collaborazione: il portale faciliterà la collaborazione fra Stati membri interessati (SMI) nel valutare una domanda di autorizzazione per sperimentazione clinica

# Regolamento (UE) 536/2014

## Impatto

- Regole e criteri identici in tutti gli Stati Membri
- Regole e criteri identici per studi profit e non-profit
- Notifica tramite portale della singola decisione per SM
- Pubblicazione tramite il portale dei dati e informazioni sui medicinali, sul loro sviluppo e processo autorizzativo
- Dettagliata descrizione del processo di submission, valutazione ed autorizzazione (artt. 4-27, 36-46)
- e-composizione dossier (Annex I-II)

# Regolamento (UE) 536/2014

## Oggi

- CT: 2 domande su base nazionale
- AIFA: singola autorità competente - autorizzazione
- CE coordinatore: parere unico
- CE satellite: parere su fattibilità
- "2 domande" "n pareri"

- Tante interazioni…..AIFA/ISS/CE/PIs/DG/Sponsor/CE/CE…

# Regolamento (UE) 536/2014

## Domani…

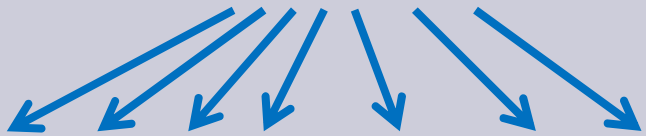
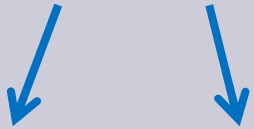
- CT: 1 domanda su base EUROPEA
- 1 singola autorità competente per SM
- 2 pareri separati per CT, ma 1 decisione per SM
- Valutazione congiunta degli Stati Membri
- 1 domanda “1 decisione”

•Interazioni…… SMR (AC/CE)/SMI - Sponsor(s)

# Cosa cambia con il nuovo Regolamento?

| Direttiva 2001/20/CE - EudraCT | Regolamento – Portal & Database |
|---|---|
| Domande multiple per una sperimentazione clinica (1 domanda per ogni SMI) / no fascicolo armonizzato | Singola domanda in formato elettronico per tutti gli SMI / fascicolo armonizzato per sperimentazione clinica |
| Valutazione individuale da parte di ogni SM senza strumento IT di collaborazione | Valutazione congiunta (tra SMI e SMR) per Parte I facilitata da strumenti IT di collaborazione |
| Doppia domanda per ogni SM: ad AC e ai CE - No singola decisione per SM (AC & CE) | 1 fascicolo di domanda al livello EUROPEO – Valutazione coordinata tra gli SM e singola decisione x SM |

# Cosa cambia con il nuovo Regolamento?

| Direttiva 2001/20/CE - EudraCT | Regolamento – Portal & database |
|---|---|
| Onere per le AC nel caricare le informazioni nel sistema | Distribuzione dell'onere tra gli utenti |
| Limitata disponibilità di dati in EudraCT per il pubblico | Accesso a tutte le informazioni relative alla sperimentazione clinica |
| Interazioni  AIFA/ISS/CE/PIs/DG/Sponsor/CEs... | Interazioni  Stati Membri (SMR/SMI) Sponsor(s) |

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# Alcuni Nuovi Aspetti


## Procedura di valutazione

- 1 REPORTING Member State – Stato membro RELATORE con funzione di coordinare la valutazione (AR)
- n… CONCERNED Member State(s) – più Stati membri INTERESSATI
- 3 fasi nella procedura: convalida/valutazione/decisione
- Parte I della relazione di valutazione => entra nel merito tecnico-scientifico qualità, non-clinica e clinica. Stato delle conoscenze, quesito clinico, ipotesi da testare, rilevanza clinica, obiettivi, endpoint, misure di sicurezza, rischio/beneficio
- Parte II della relazione di valutazione => aspetti etici e di fattibilità locale: informazioni al paziente/CI, lettera medico curante, modalità arruolamento, assicurazione, idoneità PI e Centro clinico, rimborsi

# Alcuni Nuovi Aspetti (cont.)


## Procedura di valutazione

- SM decide chi è coinvolto nella valutazione della parte I e della parte II (AC/CE) ai fini della singola decisione
- Il ruolo dei CE rimane una decisione nazionale, ma si deve assicurare la conformità con la procedura e il rispetto delle tempistiche
- E' previsto il silenzio assenso (convalida, decisione SMR, parte II)
- Processo congiunto di valutazione in una cornice Europea del nuovo Regolamento
- Si avrà necessità di stabilire una nuova modalità di interazione tra AIFA e Comitati Etici
- La normativa nazionale dovrà necessariamente essere rivista

# Alcuni Nuovi Aspetti: Procedura di valutazione in contemporanea AC/CE


Validazione

**Relazione di valutazione – Parte I***

**Valutazione coordinata (45 + 31 giorni)**

* Coinvolgimento CE?

In Parallelo

**Relazione di valutazione – Parte II****

**Valutazione nazionale (45 + 31 giorni)**

** Coinvolgimento esclusivo CE?

Notifica decisione SM

Silenzio assenso

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# Alcuni Nuovi Aspetti (cont.)


## Procedura di valutazione

- Decisione finale comunicata entro 5 giorni al Promotore dalla data di valutazione come:

-> AUTORIZZAZIONE

-> AUTORIZZAZIONE a CONDIZIONE (se le condizioni non possono essere soddisfatte al momento della domanda)

-> RIFIUTO

=> Valutazione negativa sulla Parte I: vale in TUTTI gli SM

=> Valutazione negativa Parte II: trial non autorizzato in quello SM

# Alcuni Nuovi Aspetti (cont.)


## Procedura di valutazione

- Stato membro relatore: proposto dallo Sponsor, ma la proposta è discussa tra gli SM
- Disaccordo per quanto riguarda la parte I (Opt-Out) esclusivamente in base alle seguenti motivazioni:

  a) quando un soggetto dovesse ricevere un trattamento di livello inferiore rispetto alla normale pratica clinica nello SM interessato

  b) violazione del proprio diritto nazionale

  c) osservazioni relative alla sicurezza dei soggetti e all'affidabilità e alla robustezza dei dati presentati

# Alcuni Nuovi Aspetti (cont.)


## Altri aspetti

- Tempistiche di valutazione ridotte (45 giorni !)
- …ancora il silenzio-assenso
- Più trasparenza sulle informazioni sui CTs e risultati disponibili anche in versione per il pubblico (*lay person*)
- Introduzione di SC "a basso livello di intervento"

# Alcuni Nuovi Aspetti (cont.)


## Altri aspetti

- Previste sperimentazioni cliniche in situazioni di emergenza e cluster trials
- Popolazione vulnerabile (minori, soggetti incapaci, donne in gravidanza e allattamento, persone private della libertà personale)
- Concetto di co-sponsorizzazione
- Obbligo per lo SM di garantire l'esistenza di sistemi di risarcimento danni

# Contesto Regolatorio

D.M.8/3/2003

(D. Lgs. 211/2003)

*Tissues / Cells 2004/23/EC*

*Blood 2002/98/EC*

*Paediatrics 1901/2006*

D.M. 8/2/2013

D.M. 19/03/1998 e D.M. 7/11/2008

D.M. 14/07/2009

D.M. 20/03/2008

Regolamento 536/2014

*PhVig legislation*

*ATMPs 1394/2007CE*

D.M. 17/12/2004

(D. Lgs. 200/2007)

*(Medical Devices 93/42/EC)*

D.M. 27/04/2015

(D.M. 15/11/2011)

Det. AIFA 15/06/2015

D.L. 158/2012

D.P.R. 439 21/09/2001

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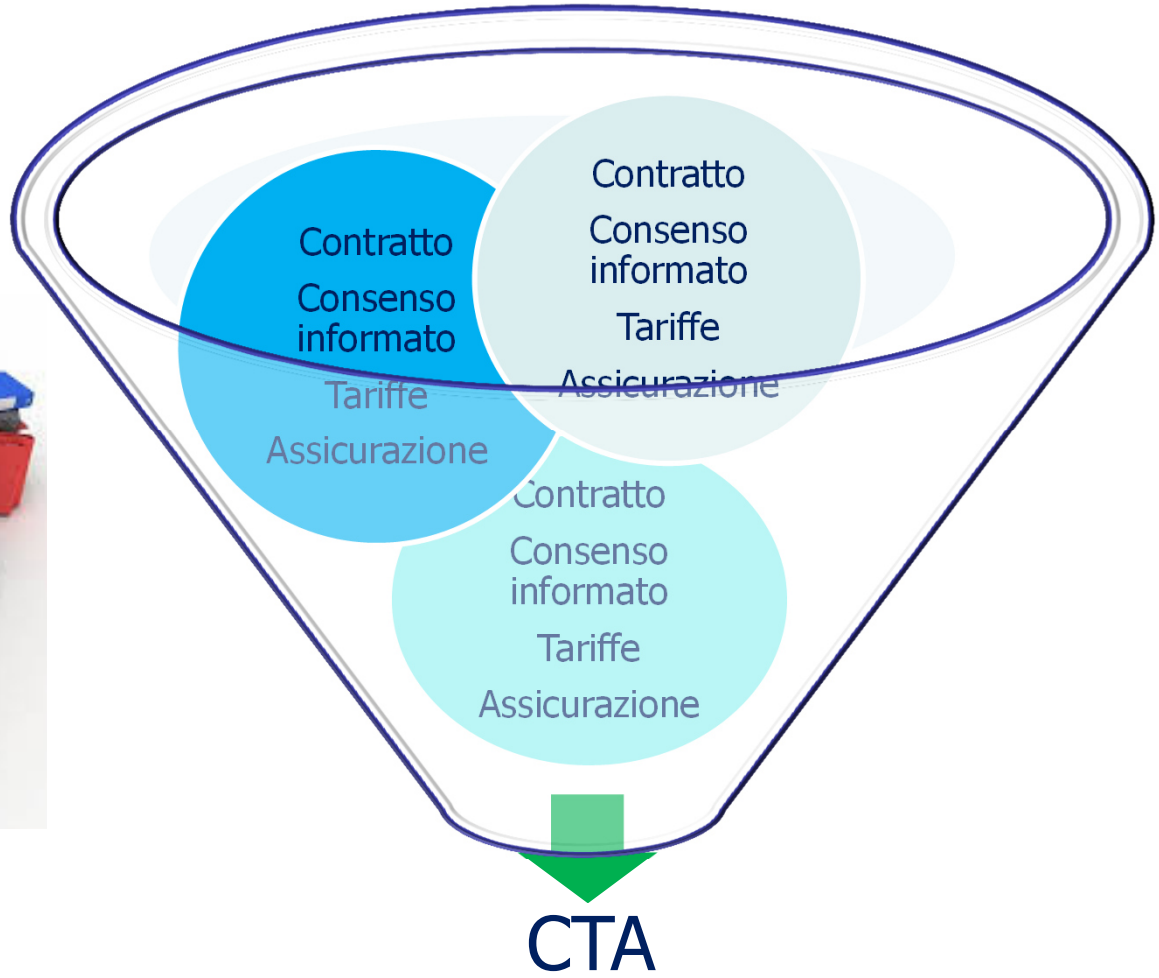
# Domanda di sperimentazione clinica…

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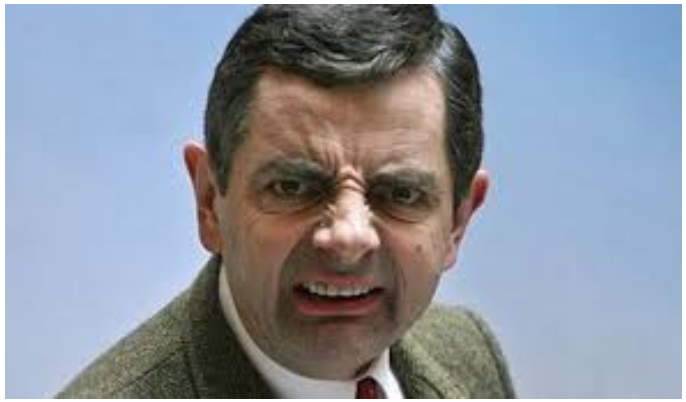
# Domanda di sperimentazione clinica…

- Contattare P.I. e sito sperimentale
- Clinical trial center: pre-valutazione
- CE: pre-valutazione
- Documentazione centro-specifica
- Versamenti tariffe centro-specifici
- Inserimento database locali
- Presentazione domanda in OsSC
- Presentazione documentazione cartacea
- Aspettare P.U…….
- Aspettare autorizzazione AIFA
- Aspettare CE satelliti
- Ricominciare daccapo per divergenze CE/AIFA…

# Avvio della sperimentazione clinica…



- Ricomincia discussione su n. xxx C.I.
- Ricomincia discussione su n. xxx contratti
- Ricomincia discussione su n. xxx contratti assicurazione
- Attesa firme contratti
- Inizio arruolamento???
- Presentazione emendamenti in ordine sparso….
- Sovrapposizione con emendamenti in altri MS….
- Riprepara tutto daccapo per gli emendamenti…..

# 2019: quanto è lontano?

- 1 contratto già firmato
- Assicurazione già definita
- 1 consenso informato
- 1 tariffa
- 1 domanda
- 1 tempistica unica
- 1 autorizzazione inclusiva di tutti i centri

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# Il Portale e Banca Dati UE

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# Agenda

- Base Legale
- Overview of “transparency rules”
- Panoramica “funzionalità Portale e Banca dati UE”
- Formazione
- UAT
- Tempistiche e *next steps*

# Base Legale

# Base Legale

L'Articolo 80 del Regolamento (UE) N. 536/2014 recita:

Portale UE

"

- L'Agenzia, in collaborazione con gli Stati membri e la Commissione, istituisce e gestisce un portale a livello di Unione che funge da unico punto di accesso per la presentazione dei dati e delle informazioni concernenti le sperimentazioni cliniche in conformità al presente regolamento. Il portale UE è di livello tecnico avanzato e di facile uso, e consente di evitare lavoro non necessario.

- I dati e le informazioni presentati mediante il portale UE sono conservati nella banca dati UE.

"

# Base Legale

L'Articolo 81 del Regolamento (UE) N. 536/2014 recita:

## Banca Dati UE

“ 1. L'agenzia, in collaborazione con gli Stati membri e la Commissione, istituisce e gestisce una banca dati UE a livello di Unione. L'Agenzia è considerata il responsabile del trattamento della banca dati UE e ha la responsabilità di evitare duplicazioni superflue tra tale banca dati UE e le banche dati EudraCT e Eudravigilance.

La banca dati UE contiene i dati e le informazioni presentati a norma del presente regolamento.

Cont…

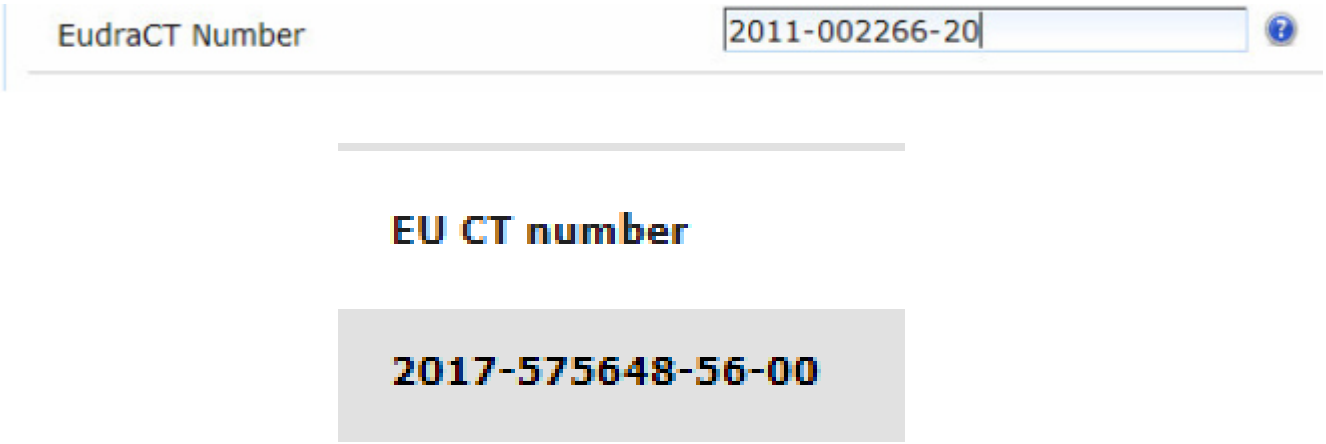
”

# Base Legale

L'Articolo 81 del Regolamento (UE) N. 536/2014 recita:

## Banca Dati UE

“ … La banca dati UE identifica ciascuna sperimentazione clinica con un numero UE della sperimentazione unico. Il promotore fa riferimento a tale numero UE della sperimentazione in qualsiasi successiva comunicazione relativa o riferita a tale sperimentazione clinica.




”

# Base Legale

L’Articolo 81 del Regolamento (UE) N. 536/2014 recita:

## Banca Dati UE

“2. L'istituzione della banca dati UE consente alle autorità competenti degli Stati membri interessati di cooperare, per quanto necessario, all'applicazione del presente regolamento e di effettuare ricerche di specifiche sperimentazioni cliniche. Facilita inoltre la comunicazione tra i promotori e gli Stati membri interessati e consente ai promotori di richiamare precedenti domande di autorizzazione a una sperimentazione clinica o a una modifica sostanziale.”

# Base Legale

L'Articolo 81 del Regolamento (UE) N. 536/2014 recita:

## Banca Dati UE

"Consente altresì ai cittadini dell'Unione di avere accesso a informazioni cliniche riguardanti i medicinali. A tal fine, tutte le informazioni contenute nella banca dati UE sono in un formato di agevole consultazione, tutti i dati collegati sono raggruppati mediante il numero UE della sperimentazione e collegamenti ipertestuali mettono in relazione dati e documenti affini presenti nella banca dati UE e in altre banche dati gestite dall'Agenzia."

# Base Legale

L'Articolo 81 del Regolamento (UE) N. 536/2014 recita:

## Banca Dati UE

"3. La banca dati UE sostiene la registrazione e la presentazione al dizionario dei medicinali contenuto nella banca dati Eudravigilance di tutti i dati sui medicinali privi di autorizzazione all'immissione in commercio nell'Unione e le sostanze non autorizzate come parte di un medicinale nell'Unione, che sono necessarie per la gestione di tale dizionario. A tale scopo, oltre che per consentire ai promotori di fare riferimento a precedenti domande, si assegna un numero UE del medicinale a ciascun medicinale privo di autorizzazione all'immissione in commercio e un codice UE della sostanza attiva a ciascuna nuova sostanza attiva non precedentemente autorizzata come parte di un medicinale nell'Unione.

Substance Management Service?

Product Management Service?"

# Base Legale

L'Articolo 81 del Regolamento (UE) N. 536/2014 recita:

## Banca Dati UE

"Ciò avviene prima o nel corso della domanda di autorizzazione alla prima sperimentazione clinica con tale medicinale o sostanza attiva, presentata a norma del presente regolamento. Tali numeri devono essere menzionati in tutte le successive domande di sperimentazioni cliniche e modifiche sostanziali.

I dati presentati in conformità del primo comma che descrivono i medicinali e le sostanze rispettano le norme dell'Unione e internazionali per l'identificazione dei medicinali e delle sostanze attive. Qualora un medicinale sperimentale abbia già un'autorizzazione all'immissione in commercio nell'UE e/o una sostanza attiva sia parte di un medicinale con un'autorizzazione all'immissione in commercio nell'Unione, i relativi numeri di prodotto e di sostanza attiva sono indicati nella domanda di sperimentazione clinica."

# Base Legale

L'Articolo 81 del Regolamento (UE) N. 536/2014 recita:

## Banca Dati UE

"4. La banca dati UE è accessibile al pubblico a meno che una parte o tutti i dati e le informazioni in essa contenute ne giustifichino la riservatezza, sulla base di una delle seguenti motivazioni:

a) protezione dei dati personali in conformità al regolamento (CE) n. 45/2001;

b) protezione di informazioni commerciali di carattere riservato, in particolare tenendo conto dello status dell'autorizzazione all'immissione in commercio del medicinale, a meno che non vi sia un interesse pubblico prevalente alla divulgazione;

c) protezione di comunicazioni riservate tra Stati membri in relazione all'elaborazione della relazione di valutazione;

d) garanzia di una vigilanza efficace degli Stati membri sulla conduzione di una sperimentazione clinica."

# Base Legale

## L'Articolo 81 del Regolamento (UE) N. 536/2014 recita:

## Banca Dati UE

"5. Fatto salvo il paragrafo 4, a meno che non vi sia un interesse pubblico prevalente alla divulgazione, i dati contenuti nel fascicolo di domanda non sono accessibili al pubblico prima che sia presa una decisione in merito alla sperimentazione clinica.

6. La banca dati UE contiene dati personali solo nella misura in cui ciò è necessario ai fini del paragrafo 2.

7.Nessun dato personale dei soggetti è accessibile al pubblico."

# Overview of transparency rules

# Overview of transparency rules

- The Legal basis for the transparency rules come from Article 81(4) of Regulation (EU) No. 536/2014 which states:
  - EU database publically accessible by default, with exceptions justified on any of the following grounds:
    - Protection of personal data;
    - Protection of commercially confidential information in particular taking into account the MA status of the medicinal product, unless there is an overriding public interest in disclosure;
    - Protecting confidential communication between MS in relation to the preparation of the assessment report;
    - Ensuring effective supervision of the conduct of a clinical trial MSs.

# Overview of transparency rules

- Only applications on which a decision has been reached will be made public;
- The default is always to make public at the first opportunity;
- All data and documents in the system will be made public with few exceptions;
- Public registration of trials at their start including all information needed for patients who may wish to participate in therapeutic or preventive trials;

# Overview of transparency rules

- Sponsors have options to defer the timing of publication of specific data/documents (use of deferrals will be monitored);
- Maximum limits are set out in the Regulation and in the addendum on transparency but shorter times can be used;
- CT Results will be published as foreseen in Regulation with exceptions for category I trials.
- The EU database shall contain personal data only insofar as this is necessary to enable cooperation between MSs and communication with the sponsor. No personal data of trial subjects should be recorded in the EU database

# Overview of transparency rules

- At the time of decision on the trial:

  - Cover letter
  - The main characteristics of the trial
    (option for deferral of a subset of this information for category 1 trials);
  - Principal investigator (PI) and their sites
  - The PI CV
  - Economic interests and institutional affiliations
  - Written statement issued by the head of the clinic/institution
  - Sponsor contact point for information on the trial and on scientific aspects
    (preferably functional roles)
  - Sponsor or MAH personal with certain legal roles

# Overview of transparency rules

- At the time of decision on the trial:

  - Assessment Report for Part I and Part II
    (option for deferral for all categories)
  - The conclusion on Part I and Part II assessment
  - disagreement on the conclusion of the assessment of Part I
  - The decision on the trial including reasons for refusal if the trial is not authorised (or where applicable the reason for its withdrawal)
  - Clinical trial related information (protocol and subject information sheet)
    (option for deferral for all categories)
  - Product related information (IB and IMPD S+E sections)
    (option for deferral for all categories)

# Overview of transparency rules

- At the start or during the trial:

  - Start date of the trial;
  - Date of the first visit of the first subject in the trial in each MS concerned;
  - End date of subject recruitment;
  - End date of the trial (per MS in the EU and globally);
  - Date of temporary halt or early termination of the trial;
  - substantial modification of the trial
  - □ (option for deferral for all categories)
  - Corrective measures.

# Overview of transparency rules

- Within 12 months from the end of the trial:
  - summary clinical trial results and lay summary (option for deferral for category 1 trials)
- 30 days after completion of the marketing authorisation process (whatever the outcome):
  - the clinical study report for trials authorised under the new Regulation and included thereafter in a MA dossier

# Overview of transparency rules

- Once assessed by MSs (option for deferral for category 1 trials):
  - urgent safety measures & unexpected events
  - serious breaches
- At the end of the procedure (option for deferral for category 1 trials):
  - inspection report from third countries authorities relating to EU sites and trials.
  - Union controls
  - Inspection Reports

# Categories

| CATEGORY 1 | CATEGORY 2 | CATEGORY 3 |
|---|---|---|

The publication of some information from the EU Portal and Database will be deferred.

The length of this deferral is dependent on the trial's categorisation.

Exceptions to the transparency are the paediatric trials (all phases) which still need to be submitted within 6 months to NCAs and should be published as per Regulation (EC) No 1901/2006: this has not been amended by the CT regulation.

# Categories

| CATEGORY 1 | CATEGORY 2 | CATEGORY 3 |
|---|---|---|
| Pharmaceutical development clinical trials | Therapeutic exploratory and confirmatory clinical trials | Therapeutic use clinical trials |
| • Phase I trials<br>• Phase "0" trials<br>• Bioequivalence and bioavailability trials<br>• Similarity trials for biosimilar products<br>• Other trials to determine equivalence | • Phase II trials<br>• Phase III trials | • Phase IV<br>• Low-intervention clinical trials |

# Categories

| Section of trial document | | CATEGORY 1 | CATEGORY 2 | CATEGORY 3 |
|---|---|---|---|---|
| **Main Characteristics of the trial** | | For a subset of information and **up to the time the CT Results Summary** is posted (Justification) | No deferral | No deferral |
| **Trial related documents** | Subject Information sheet | Up to the **time of MA** using this trial **or up to 7 years** after the end of the trial, whichever is earlier | Up to the **time of MA** using this trial **or up to 5 years** after the end of the trial, whichever is earlier | No deferral |
| | Protocol | | | **Up to the time the CT Results Summary** is posted (usually 12 months after the end of the trial in the EU) |
| **Product related Documents** | IB | | | |
| | IMPD, S&E | | | |
| **Assessors documents / data** | Request for information | MS decides but takes into account the exceptions of the legislation and the deferral time proposed by the sponsor | | No deferral |
| | Assessment Report (I&II) | | | |
| | Conditions | | | |

# Categories

| Section of trial document | | CATEGORY 1 | CATEGORY 2 | CATEGORY 3 |
|---|---|---|---|---|
| **Substantial Modification** | | Deferral possible only for changes or additions to data/documents not yet made public because of the legal deadline is not reached or a deferral was requested. Publication will take place **when the legal deadline is reached or deferral deadline expires.** | | |
| **Notifications** | Unexpected events, urgent safety measures | **Up to the time when summary results are posted** - except for early terminations for reasons involving subject safety or if Corrective measures (Justification) | No deferral | No deferral |
| **Clinical Trials Summary Results** | Scientific Summary | Up to **18 months after the due date for the publication of the summary of results** (usually 12 months after the end of the trial unless article 37(4) applies) (Justification) | No deferral | No deferral |
| | Lay person | | No deferral | No deferral |
| **Clinical Study Report** | | No deferral | No deferral | No deferral |

# Categories

| Section of trial document | | CATEGORY 1 | CATEGORY 2 | CATEGORY 3 |
|---|---|---|---|---|
| **Supervisory measures** | Serious Breaches | If the sponsor requested a deferral up to the time of publication of summary results the same will apply here. | No deferral | No deferral |
| | Inspections Reports (EU) | | | |
| | Inspections Reports (by third country CA) | | | |
| **Supervisory measures** | Union Controls | | | |
| | Corrective Measures | No deferral | | |

# Overview of transparency rules

- The IMPD quality section will not be made public as it remains commercially confidential even after the marketing authorisation has been given
- Draft assessment reports (outside the EU database)
- Names of the Member States experts (outside the EU database)
- Personal information identifying sponsor staff (protection personal data)
- Personal information identifying MAH/applicant (protection personal data)
- Direct contacts of clinical investigators, sponsors or MAH personnel (protection personal data)
- Agreements between the sponsor and the investigator site

# Overview of transparency rules

- Generate trust – information is available;
- Build confidence – I understand what is happening;
- Empower – knowledge enables decision-making.

# Panoramica “funzionalità Portale e Banca dati UE”

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# EU Portal: EMA

- EMA deve fornire, gestire, ed aggiornare le piattaforme informatiche in collaborazione con gli Stati membri e la Commissione, così come espresso nel Regolamento
  - EU Portal e database (Art. 80, 81, 82 e 84)
  - Safety Reporting (Art. 40 e 44)
  - EudraCT e fase transitoria (Art. 98)

- Database UE deve essere accessibile pubblicamente, nel rispetto del diritto alla protezione dei dati di carattere personale, deve permettere comunicazioni confidenziali tra SM, assicurare supervisione delle sperimentazioni cliniche

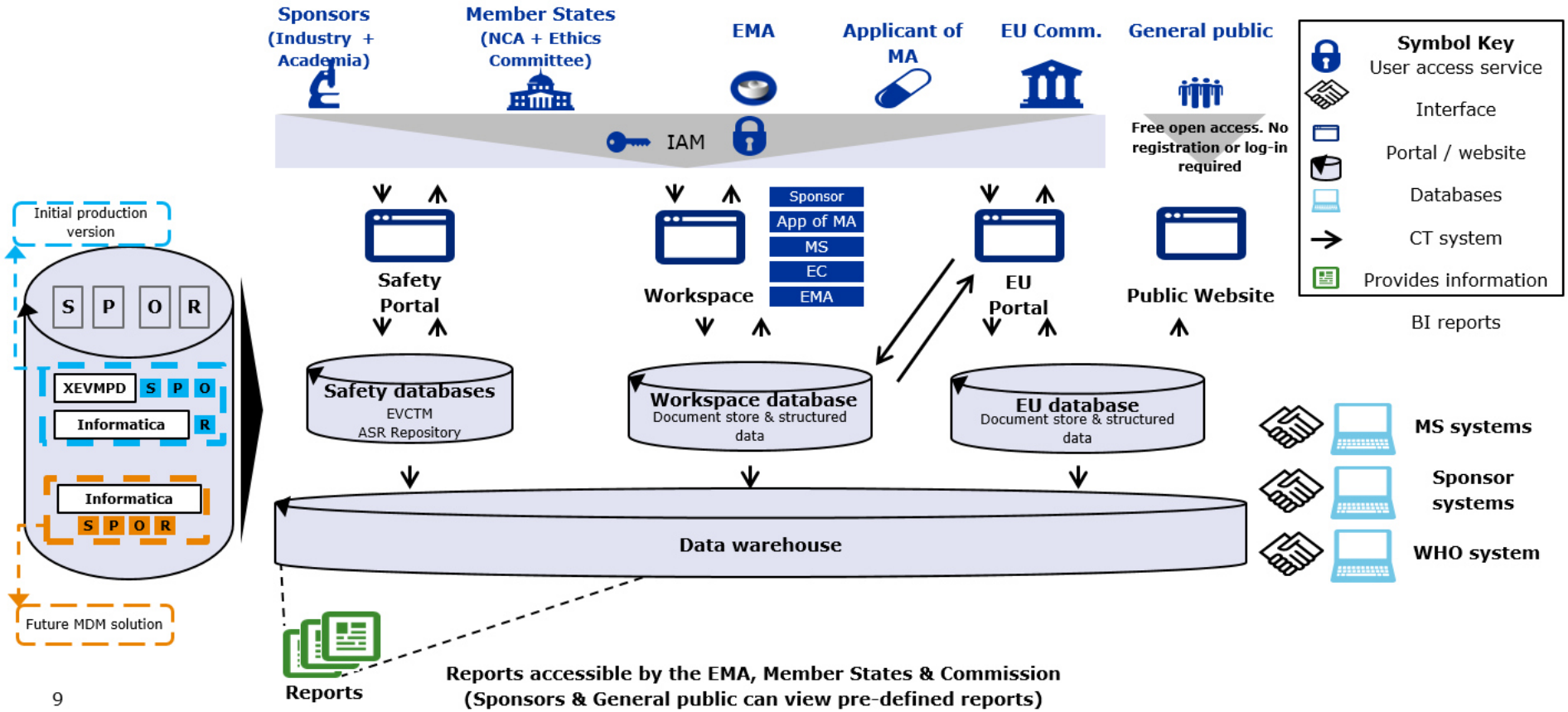
# EU Portal: EMA

- Il progetto si propone di sviluppare un portale UE, che verrà utilizzato quale singolo punto di accesso per presentare dati e informazioni inerenti le sperimentazioni cliniche in accordo al Regolamento
- Il progetto svilupperà inoltre un database per l'archiviazione dei dati e delle informazioni inserite tramite il portale. I dati del database saranno resi pubblici.
- E' contemplato l'allestimento di una piattaforma di lavoro e archivio di documenti per diversi *stakeholders* al fine di permettere la gestione documentale, l'interazione/collaborazione nel corso del ciclo di vita della sperimentazione clinica

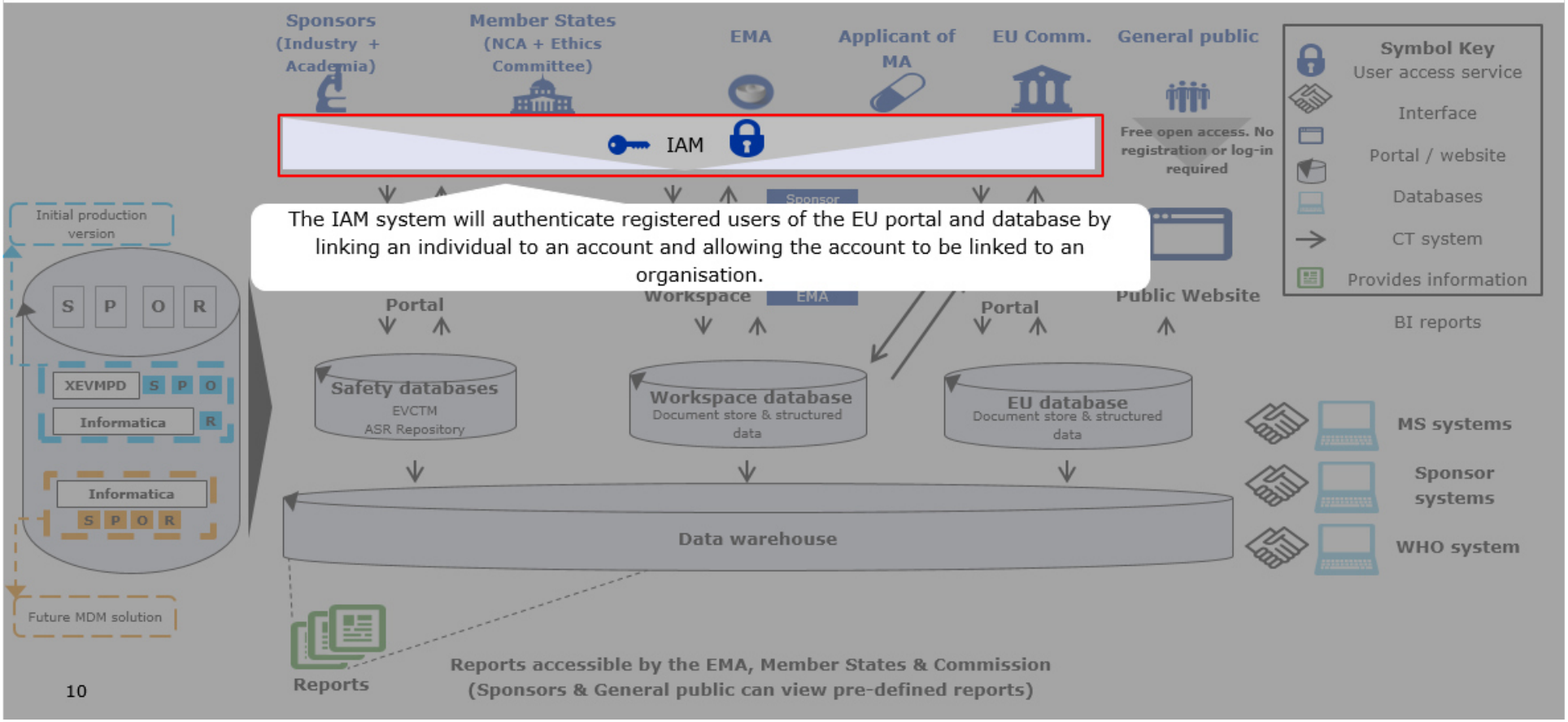
# EU Portal: EMA

- Il Regolamento 536/2014 (Art. 82) delinea i requisiti legali per il portale e la banca dati UE
- Per sviluppare il sistema, l'EMA in consultazione con gli SM, *Stakeholders* e Commissione ha sviluppato un catalogo di requisiti e un flusso di processi
- Sulla base dei requisiti legali, le specifiche funzionali vengono elaborate, delineando le funzionalità del sistema soggette a ispezione
- Il catalogo include, ma non si limita alle funzionalità oggetto di ispezione

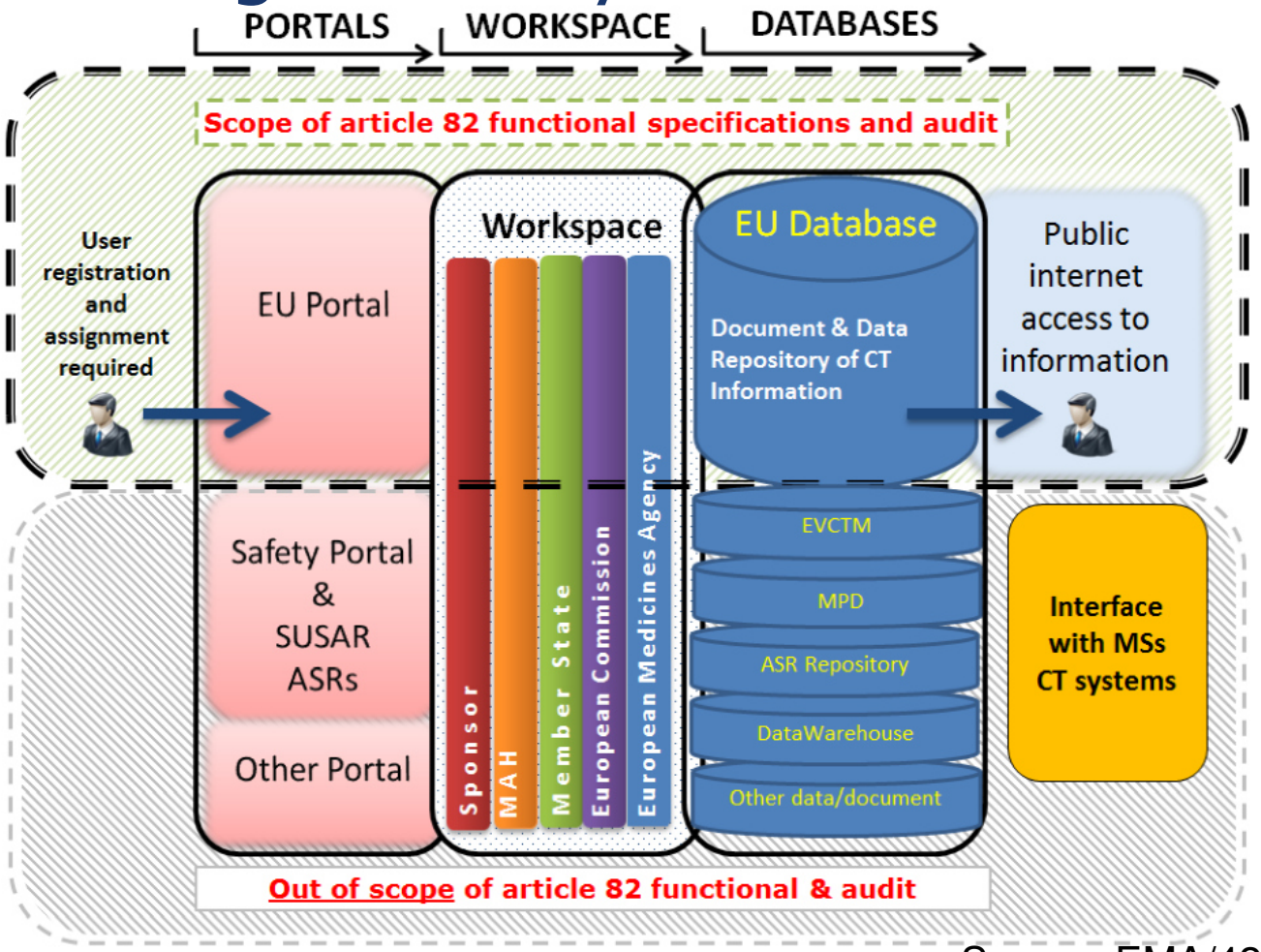
This diagram depicts the To-Be system architecture for the submission of Clinical Trial Application Dossiers and Results:



This diagram highlights how the EU portal and database will interact with the Identity Access Management (IAM) solution:



# High level System Overview




Source: EMA/42176/2014 Rev. 1

# API version 1

- API = Application Programming Interface.
  This is a "computer to computer" interface between computer systems.
- There are three must requirements which must be fulfilled by the version 1 of the API for the audit.

| Req. ID | Req. name | Notes | MoSCoW |
|---|---|---|---|
| R02.03.01 | Interface to circulate draft assessment report part I | Only the RMS shall be able to circulate a draft assessment report part I through the workspace using a system interface. | M |
| R02.03.02 | Interface to submit assessment report part I and II | Only the RMS shall be able to submit final assessment report part I through a system interface to the database. The MSC shall be able to submit the final assessment report part II through a system interface to the database. | M |
| R04.01.73 | MSC interface to export notifications | The MSC shall be able to export notifications (submitted through the EU portal to the database) to their own systems using a system interface. | S |
| R08.07.07 | System interface to register MS organisation | Member states shall be able to register member state organisations using a system interface. | C |
| R09.01.04 | MS interface to download clinical trial information | Member States, EMA and EC shall be able to export/download a clinical trial application using a system interface. | M |

# High level System Overview

**Submission Workspace - Sponsor**

| | |
|---|---|
| CT Overview & Search | • Search for trials I have access<br>• See current state of my trials<br>• Select & Initiate new / change / notification of trial |
| CT Application Dossier | • Complete application dossier for new / updated trial (Initial, Modification, Notification)<br>• See/compare versions of a Trial (Each Submission creates a version)<br>• Invite other users to participate in application preparation |
| Requests for Information & Notices | • See formal or informal requests for information & respond<br>• See deadlines for requests<br>• See all alerts and notices for all my trials |

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Source: EMA October 2015

# High level System Overview

Public Website – Public, EMA, MSCs

| | |
|---|---|
| Entry Site | •News, Announcements, scheduled downtimes,…<br>•Register or log in to the CT System |
| Public Search | •Search for keywords and filter results<br>•Find public clinical trials. The same portal also contains pro active publications, medicinal products, articles,… |
| Public CT | •Go into the detail of a clinical trial<br>•Download trial information and documents |
| Content Mgmt (EMA) | •Supervise published content of trials<br>•Comment on publications |

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Source: EMA October 2015

# High level System Overview

## Authority Workspace - Authorities

**Tasklist**

- An overview of all tasks to be done by me or my group
- See all deadlines, for all my tasks
- Able to open a specific item to see the task details

**Tasks**

- Forms specific to the type of work that has to be done (e.g. select RMS, document considerations, make a decision…)
- Able to open the details of the clinical trial dossier
- Collaboration:
  - Write considerations / comment against part one and two
  - Formal or informal Request for Information to the sponsor
  - Delegate Task, Create subtask and involve more people from this MSC (e.g. ethics committee).

Source: EMA October 2015

# High level System Overview

**Authority Workspace - Authorities**

**Clinical Trial**

- An overview of one trial including: the application dossier, medicinal product, documents, status, timetable, associated tasks, version history
- Option to start a MS notification (e.g. corrective measure)

**CT Overview & Search**

- A search for all clinical trials. Documents are restricted to MSC.

**Docs**

- Download documents submitted by the sponsor
- Upload documents
  - For national purposes
  - For all MSCs to see
  - To the EU Database (sponsor & later public)

Source: EMA October 2015

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# High level System Overview

Authority Workspace - Authorities

**Inspection**

- Create new inspections linked to sites and clinical trials

**System Interfaces**

- A service interface (CRUD) is used for all entities. The majority will be exposed in the EudraNet for MSCs to consume. E.g.:
  - Read trial
  - Create, read, update Document to trial,…
- The specific interfaces will be specified during the implementation

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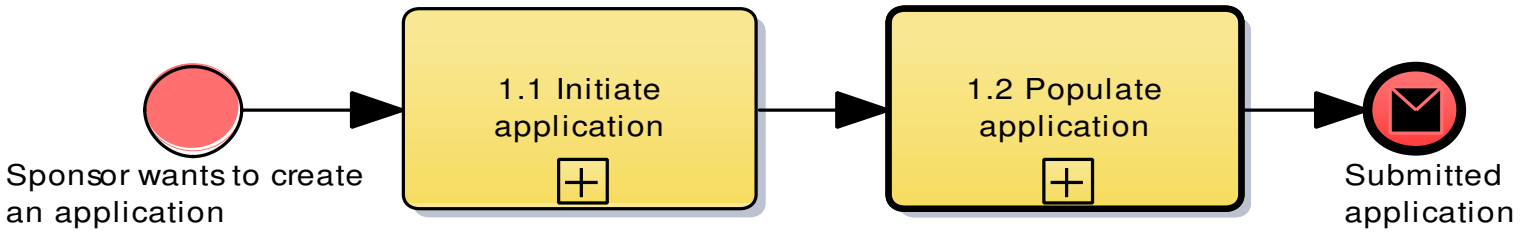
Source: EMA October 2015

# Esempio di Processo

- Create an application

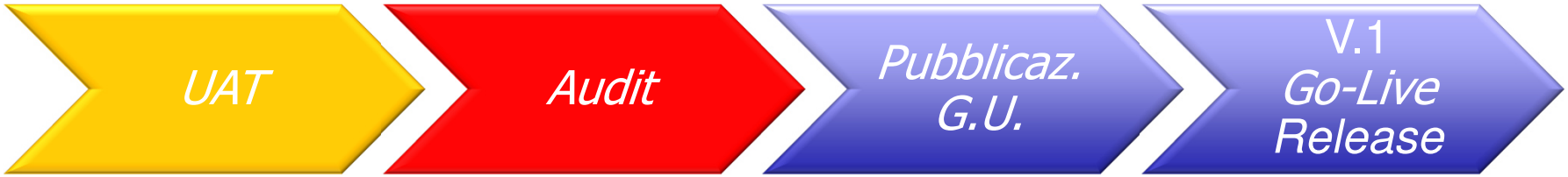



| BUSINESS PROCESS | USE_CASE | REQUIR. NAME | REQUIR. REFERENCE | REQUIR. AUDIT FLAG |
|---|---|---|---|---|
| 1.1 Initiate application | Create new initial application | Select Sponsor | Article 71, Annex I, Functional Spec., Sect. 6 (1.1, 3.2) | Yes |
| 1.2 Populate application | Upload CTA document | Upload of a document | Functional Spec., Sect. 6 (3.6) | Yes |

# Stato del Progetto


- Raccolta e analisi dei requisiti ultimata
- EMA ha sviluppato un modello di *business* con processi consolidati in consultazione con gli SM e stakeholders e si è completata la revisione interna da parte di EMA
- Il catalogo dei requisiti ha subito la revisione interna di EMA e viene utilizzato come scheletro per la preparazione degli *use cases*
- La specifica degli *use cases* è in corso…

# Stato del Progetto




- User Acceptance Tests (UAT)
- Audit indipendente sulle specifiche funzionali
- EMA informerà la Commissione dell'esito dell'Audit, la quale, pubblicherà un avviso in GU dell'UE, a conferma appunto della piena funzionalità del sistema
- Rilascio della Versione 1 *Go-Live e* applicazione del Regolamento

# Training principles and approach

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| Online training | Face - to - face | Training colleagues | On-going support |
|---|---|---|---|
| **Details** | **Details** | **Details** | **Details** |
| • Enable submission of dossier in 1 day<br>• Online material (videos, test environment, User manuals, Guidance documents) | • Tailored training of **Lead trainers**<br>• Provided by training concessionaire<br>• 2-3 days for commercial sponsors<br>• 1 day for SME's & non-commercial sponsors | • **Lead trainers** use knowledge and online material to train colleagues<br>• Online material includes videos, test environment, | • The EMA provides on- going support through Webinars, Query management, etc. |
| **Targeted at:** | **Targeted at:** | **Targeted at:** | **Targeted at:** |
| • All stakeholders<br>Primary focus of training | • Large commercial sponsors<br>• SME's<br>• Non-commercial sponsors<br>• Member States | • Large commercial sponsors<br>• SME's<br>• Non-commercial sponsors<br>• Member States | • All stakeholders |

# User Acceptance Tests

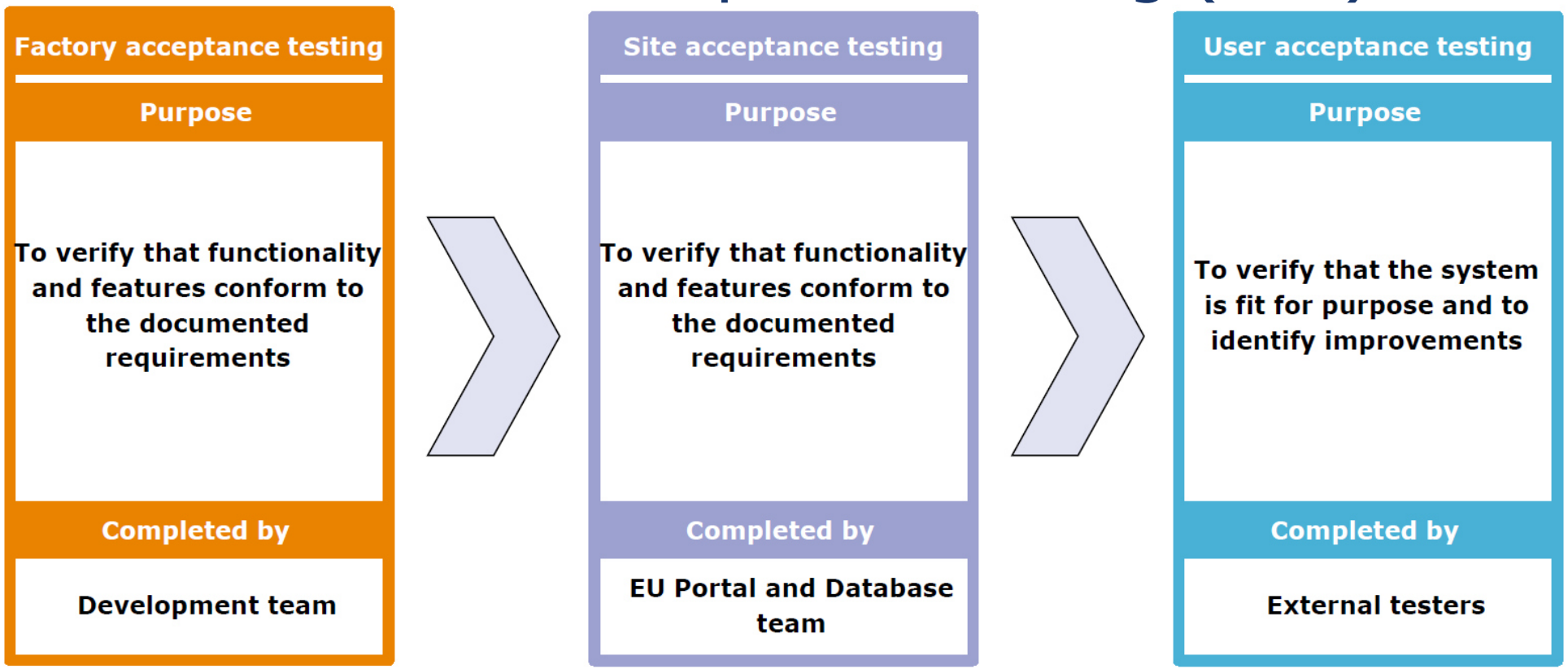
# What is User Acceptance Testing (UAT)?

- UAT is the validation of business functions and the system flow against business requirements
- UAT is carried out by end users of the system
- Other types of testing are carried out prior to UAT. These verify that the functionality and features of the system conform to the documented requirements
- UAT is planned to be carried out every three months within the CT programme

UAT verifies the system has the right features

Other test types verify the system has no significant bugs

# What is User Acceptance Testing (UAT)?

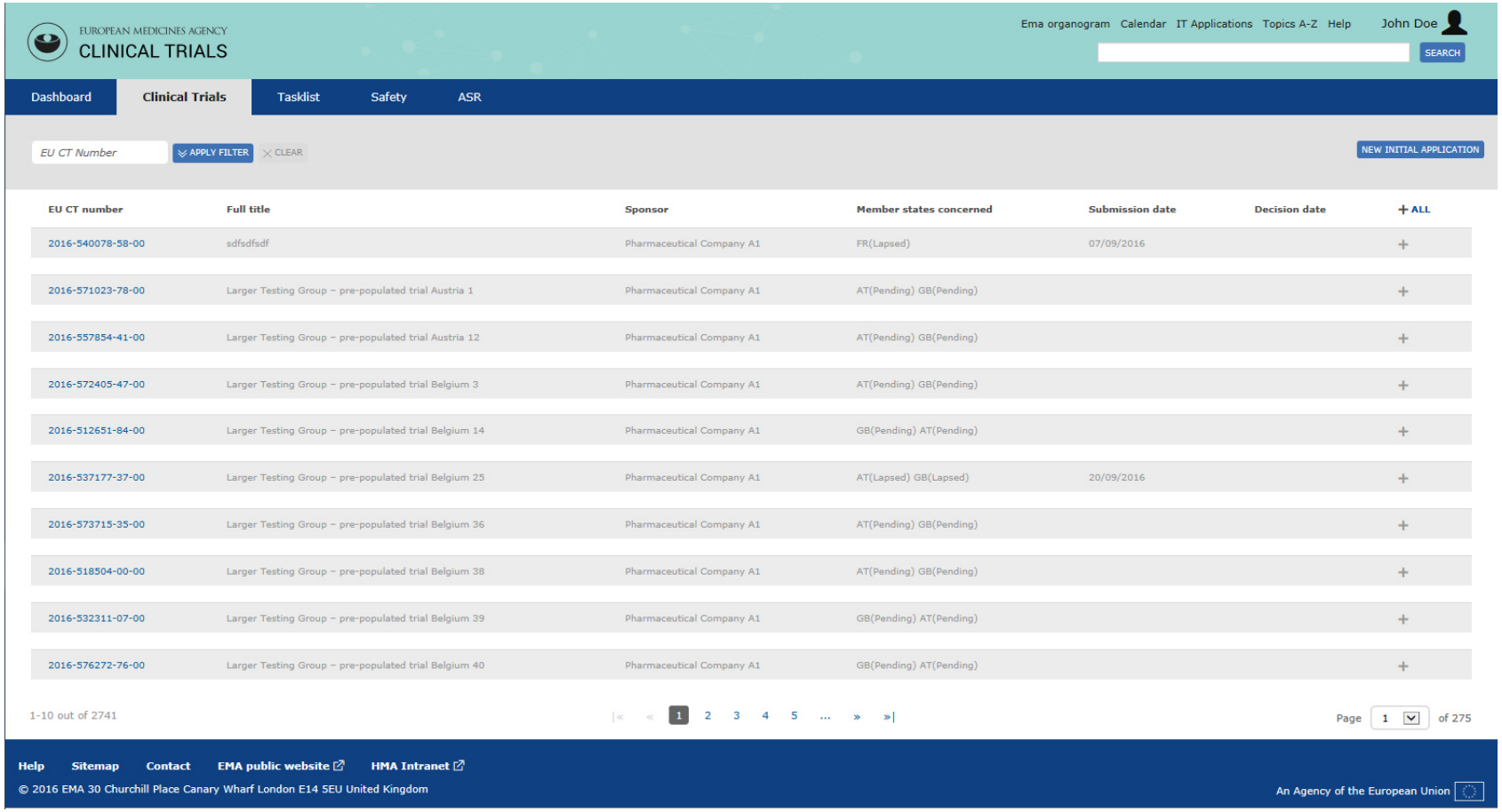



The purpose of UAT is to verify that the system is fit for purpose. Before each user acceptance test a series of internal tests are conducted to verify that there are no significant bugs.

# Dettaglio UAT

- Suggested improvements – proposte di miglioramento del sistema, all'interno di quanto già definito nelle specifiche funzionali;
- Bug – un comportamento del sistema che non rispecchia le specifiche definite;
- CT Change (CT Change Request) – proposte di cambiamento nel sistema, rispetto alle specifiche già definite;

# Screenshot - dettaglio UAT

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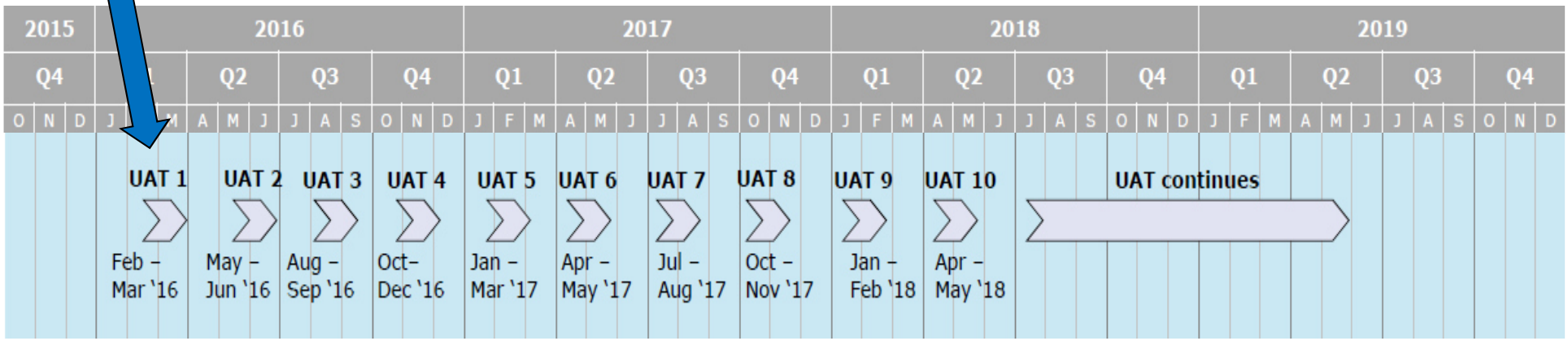
# Dettaglio UAT



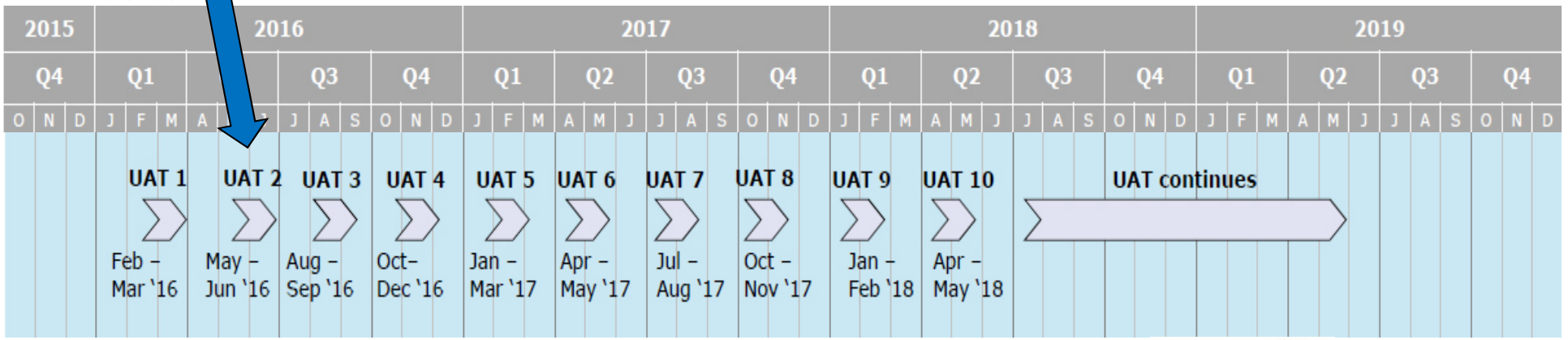

## UAT 1

- 11 - 17 marzo 2016
- 43 organizzazioni
  (27 SM + 16 Stakeholder)

- Contributo AIFA
  Team di 10 tester
  32 commenti + 15 feedback
  -> Totale 47 segnalazioni

| Issue Category | Number of Issues Raised |
|---|---|
| Suggested improvement | 8 |
| Bug | 7 |
| Existing requirement | 4 |
| **Total** | **19** |

# Dettaglio UAT




## UAT 2

- 13 - 20 giugno 2016
- 45 organizzazioni (28 Stati Membri, 16 Stakeholder e la Commissione Europea)
- Contributo AIFA
  Team di 12 tester

| Issue Category | Number of Issues Raised* |
|---|---|
| Suggested improvement | 15 |
| Bug | 13 |
| CT Change | 7 |
| **Total** | **35** |

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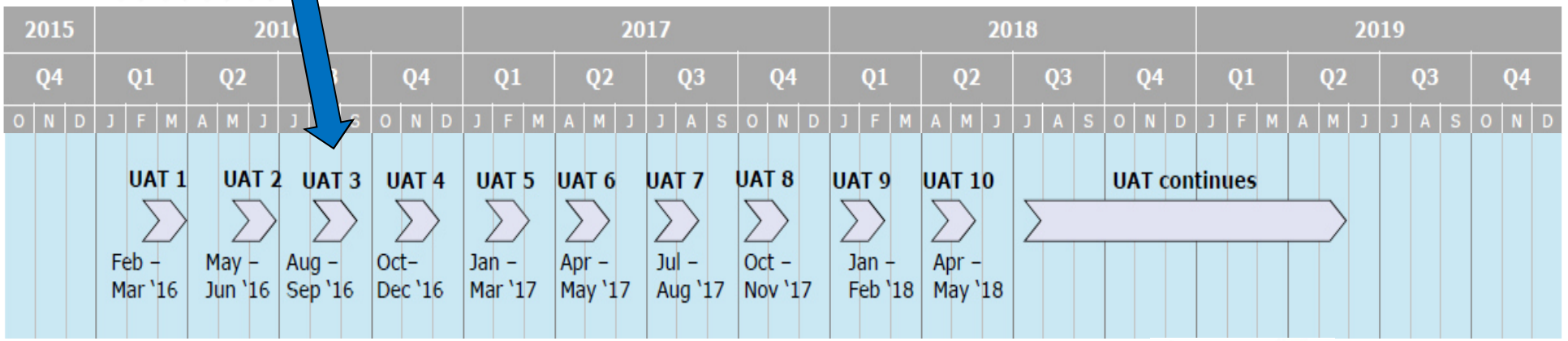
# Dettaglio UAT




## UAT 3

- 19 - 26 settembre 2016
- 2 Gruppi: Large Group Testing + Small Group Testing (MS-Sponsor)
- Contributo AIFA
- Team di 14 tester

| Issue Category | Number of Issues Raised* |
|---|---|
| Suggest Improvements | 13 |
| Bugs | 8 |
| CT Change | 8 |
| **Total** | **29** |

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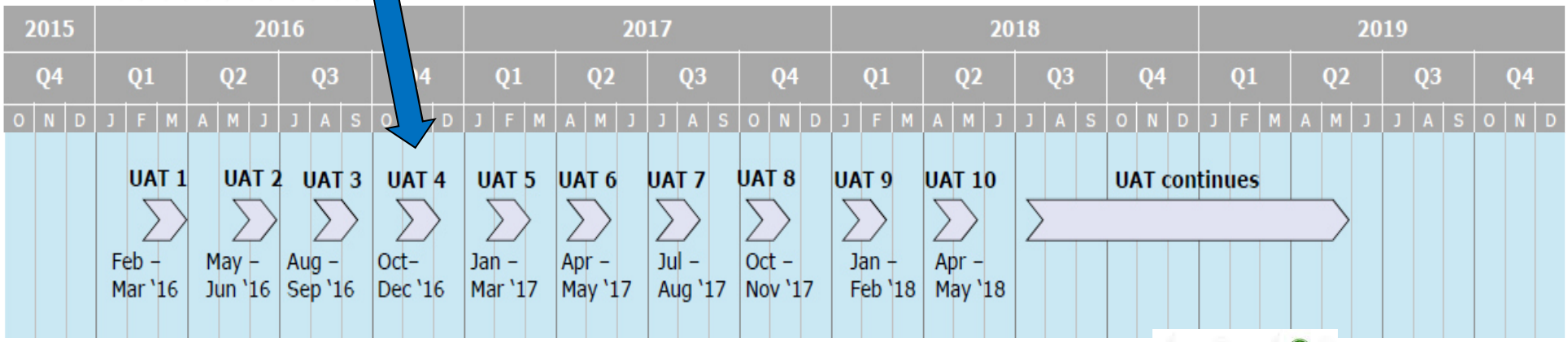
# Dettaglio UAT




## UAT 4

- 24 novembre – 2 dicembre 2016
- 1 Gruppo: Large Group Testing

- Contributo AIFA
- Team di 14 tester

| Issue Category | Number of Issues Raised* |
|---|---|
| Suggested Improvements | 48 |
| Bugs | 13 |
| CT Change | 10 |
| **Total** | **71** |

**Figure 14: Number of issues raised by category**

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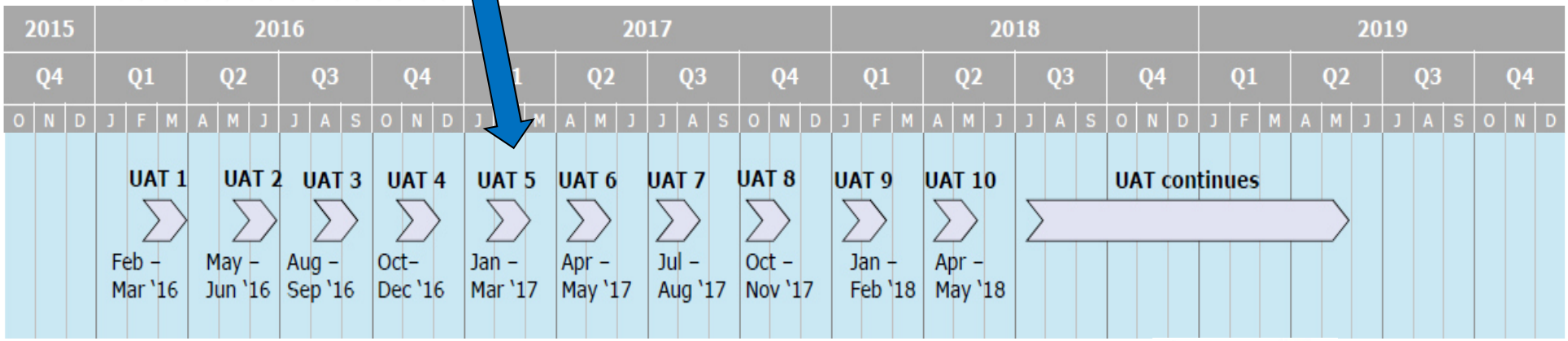
# Dettaglio UAT




## UAT 5

- 28 febbraio – 8 marzo 2017

- Contributo AIFA 2 gruppi
- Testers group
- Freeform test submission

| Issue Category | Number of Issues Raised* |
|---|---|
| Bugs | 30 |
| Suggested Improvements | 28 |
| CT Change | 10 |
| **Total** | **68** |

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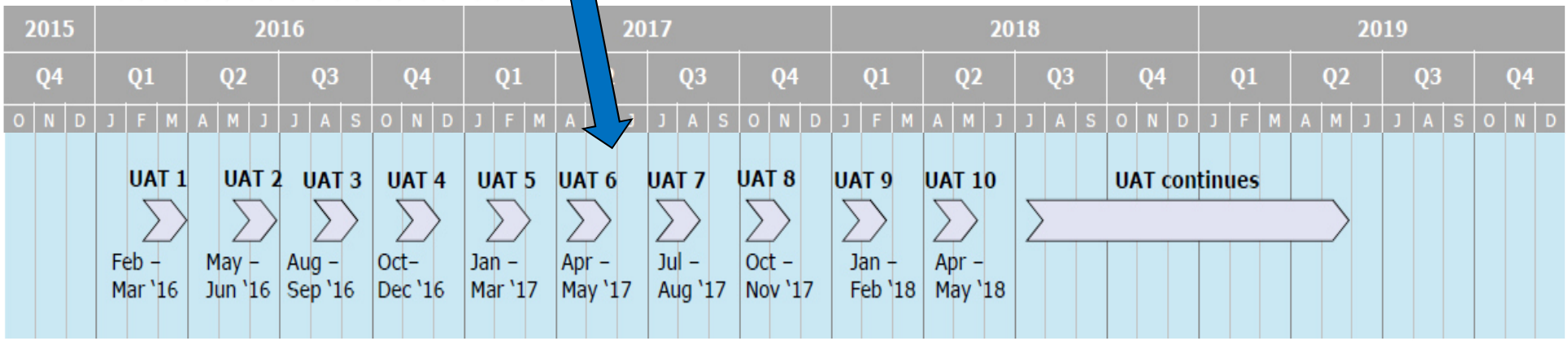
# Dettaglio UAT




## UAT 6

- 29 May to Friday 02 June
- On Site Testing at EMA Facilities

- Contributo AIFA
- 1 on site tester
- Testers Group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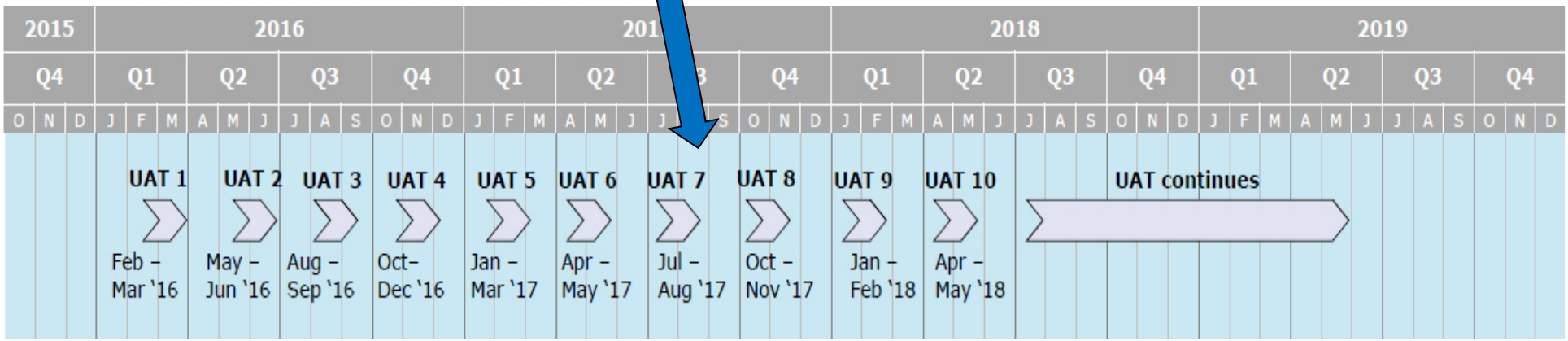
# Dettaglio UAT




## UAT 7

- 29 August to Friday 1 September
- On Site Testing at EMA Facilities

- Contributo AIFA
- 1 on site tester
- Testers Group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# Tempistiche e *Next Steps*

# Revised Timelines

- Development of EUPD is severely delayed and significant quality issues have been identified
- These can be traced back to specific root causes and the supplier is taking measures to address shortcomings in delivery speed and quality and has elaborated a new development schedule
- These measures are expected to improve delivery from both aspects

# Revised Timelines

- The new development schedule proposed leads to a delay in the *Audit* from August 2017 to *April-May 2018*
- Assuming a MB decision at the October 2017 meeting, the Regulation would become applicable on *July 2019?*
- The MB will decide on the acceptance of the revised delivery timeframe in the October 2017 meeting, once progress with development has been confirmed

## Implementation (updated)

Although the Regulation was adopted and entered into force in 2014, the timing of its application depends on **confirmation of full functionality** of the EU portal and database through an independent audit. The Regulation becomes applicable six months after the European Commission publishes notice of this confirmation.

EMA's Management Board endorsed a delivery timeframe in December 2015. However, due to technical difficulties with the development of the IT systems, the portal's go-live date has to be **postponed**.

EMA's Management Board will discuss a **new delivery time frame** in October 2017 once the developer confirms progress.

Due to these delays, the **EU Clinical Trial Regulation** will come into application during 2019 instead of October 2018, as previously scheduled.

For more information on the original delivery timeframe, see:

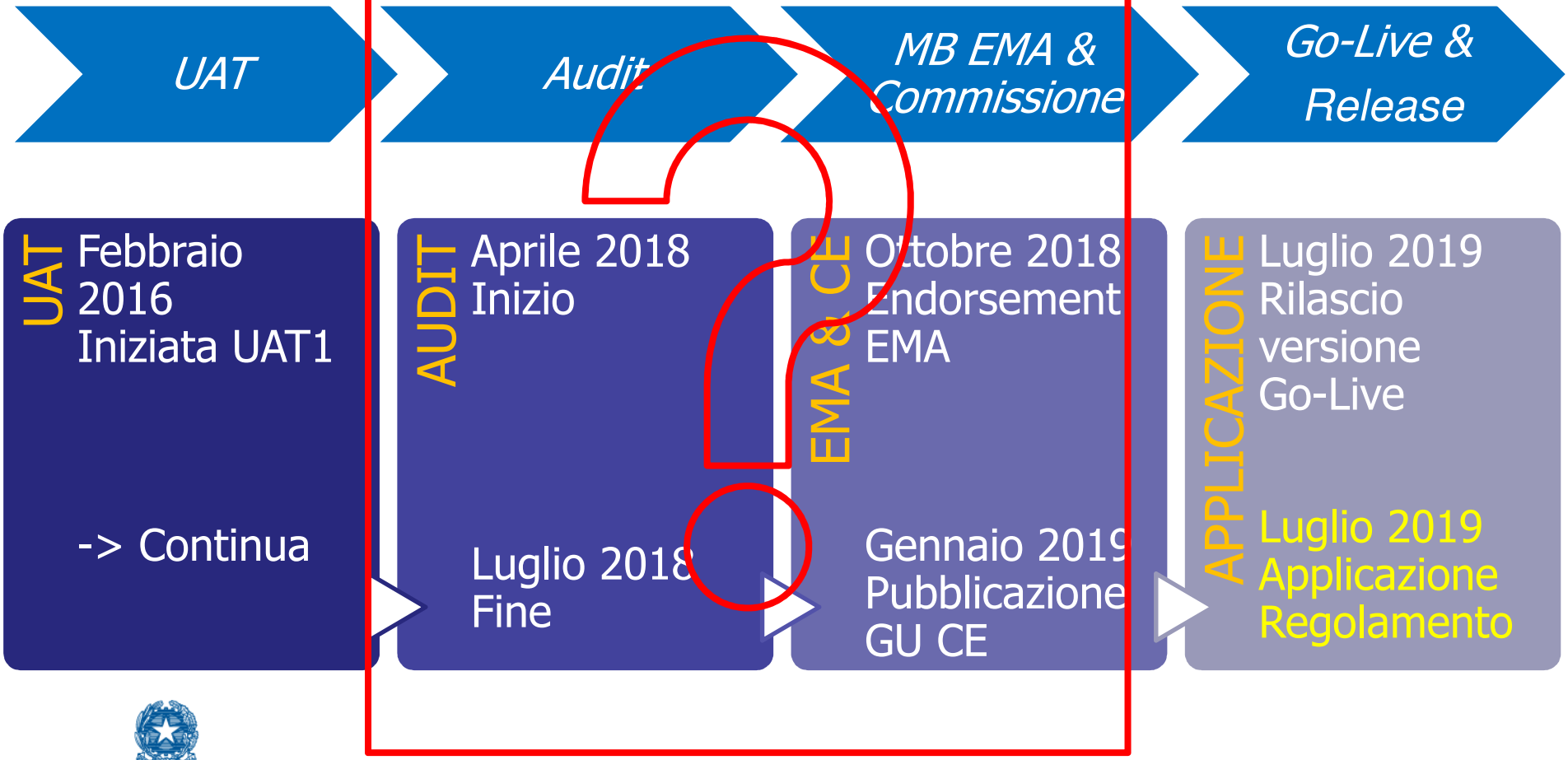
- Delivery time frame for the EU portal and EU database

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp

# Revised Timelines

| | |
|---|---|
| September 2015 | • V.1 Go live Oct. 2017<br>• Regulation applicable Dec. 2017 |
| March 2016 | • V.1 Go live Sep. 2018<br>• Regulation applicable Oct. 2018 |
| October 2017 | • V.1 Go live Jul. 2019?<br>• Regulation applicable Jul. 2019? |

# Tempistiche Portale & Database UE

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# Tempistiche Portale & Database UE


Aprile 2018: audit indipendente

Ottobre 2018: Endorsement EMA

Gennaio 2019: avviso pubblicato su G.U. UE

Luglio 2019: applicazione Regolamento n. 536/2014

# Tempistiche – dettaglio milestones

| 2017 | | | | 2018 | | | | 2019 | | | | 2020 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 |
| J F M | A M J | J A S | O N D | J F M | A M J | J A S | O N D | J F M | A M J | J A S | O N D | J F M |

OGGI

10 mesi


Aprile-Luglio 2018

~ 2 Anni


Luglio 2019

# Next Steps: in attesa del portale…

- È istituito un gruppo di coordinamento e consultivo della Commissione Europea per le sperimentazioni cliniche (Clinical Trials Coordination and Advisory Group, CTAG), composto dai referenti nazionali

- Clinical Trials Facilitation Group (HMA)

  Principalmente coinvolto nel coordinamento dell'attuale Voluntary Harmonisation Procedure - VHP

- Gruppi di lavoro EMA sul Portale e database UE:

  EU Clinical Trials portal and Union database meeting with Member States / Experts / Stakeholders

# CTFG: aspettando il portale

- La discussione fra gli Stati membri al fine di raggiungere un approccio armonizzato per quanto concerne i principali aspetti del Regolamento e dell' applicazione nazionale è in corso…
  - Quale sarà l'organizzazione a livello nazionale per la parte I, parte II, decisione, appello?
  - Come verranno assegnate le responsabilità?
  - Come strutturare le interazioni tra i diversi interlocutori?
- Condivisione di approccio comune tra gli Stati membri su alcuni interrogativi

# CTFG: aspettando il portale

- L'Autorità Competente sarà il punto di contatto nazionale, responsabile per la redazione della relazione di valutazione inerente la parte I, e la valutazione della parte II sarà principalmente sotto la responsabilità del Comitato Etico
- Input potenziale da parte del Comitato Etico sulla parte I ancora da definirsi nella maggior parte degli Stati membri
- La Decisione finale rifletterà la posizione consolidata dell' Autorità Competente e del Comitato Etico e sarà comunicata tramite il portale da parte dell' Autorità Competente
- Entrambe le relazioni di valutazione sulla parte I e sulla parte II verranno caricate nel Portale UE dalla Autorità Competente

# MS & Expert Forum: aspettando il portale

- Accreditamento al portale potrà avvenire a vari livelli
- Lo Sponsor non potrà delegare i CE ad operare nel sistema
- Solo gli SM avranno potere di delega e la delega sarà su base utente
  - Nel caso pertanto in cui uno SM decidesse di fornire accesso ai CE, i CE dovrebbero accreditarsi, sarebbe poi lo SM ad avere l'onere di delega per ogni singolo utente (accesso per singola sperimentazione clinica o generico?), e la responsabilità nel verificarne i requisiti, nonché mantenere una lista di utenti aggiornata per ogni CE

# MS & Expert Forum: aspettando il portale

- Interazione Sponsor – SM: lo Sponsor potrà interagire tramite portale solo con gli SM, il dialogo con i CE passerebbe pertanto attraverso lo SM, di cui i CE sono considerati parte integrante
- Formato della relazione di valutazione della parte I sarà verosimilmente "web-based"
- Se ci sarà input da parte dei CE sulla parte I, come bisognerà veicolarlo? (potenziale ruolo OsSC?)
- Formato della relazione di valutazione della parte II verosimilmente "pdf" – da costruire su base nazionale (potenziale ruolo OsSC?)

# MS & Expert Forum: aspettando il portale

- Ogni MS dovrà organizzare la valutazione della Parte II in collaborazione con i CE in maniera autonoma (fuori dal portale – potenziale ruolo OsSC?)
- In discussione il collegamento portale ⟷ sistemi IT nazionali per trasferimento bidirezionale dei dati
- Informazioni sulle sperimentazioni cliniche in UE saranno accessibili tramite il portale, per le informazioni sulle sperimentazioni in Italia è ipotizzabile un ruolo dell' OsSC

# OsSC e potenziali sviluppi

- Quale la situazione in merito ai sistemi IT nazionali? Basarsi esclusivamente sul Portale o pianificare cambiamenti/sviluppi del sistema IT nazionale?
- Gli SM stanno tutti prendendo in considerazione l'opportunità di avere piattaforme IT nazionali per supplire alle funzionalità che il portale non garantisce
- Resta ancora da definire quali attori avranno accesso, a quali dati e con quali modalità
- Non è possibile al momento dare una risposta esaustiva, fintanto che maggiori dettagli sul Portale UE saranno resi disponibili dall' EMA

# OsSC e potenziali sviluppi

- In linea di massima il sistema IT nazionale dovrebbe essere necessario per assistere nella gestione del flusso di lavoro, redazione della relazione di valutazione e nell'interazione tra Autorità Competente e Comitati Etici
- Fondamentale rispettare i principi di confidenzialità e contestualmente garantire il diritto di accesso ai dati
- Con tutti i suoi difetti, l'OsSC ci mette in posizione di vantaggio (esiste e abbiamo circa due anni per consolidarlo e svilupparlo)
- In quest'ottica, AIFA ha avviato un dialogo con gli "stakeholder" per valutare opinioni e possibili scenari di sviluppo per l' OsSC

# OsSC e potenziali sviluppi

- Indentificazione singolo Comitato Etico
- Dialogo ed interazione AIFA ⟷ Comitato Etico
- Input su relazione di valutazione della parte I
- Produzione e condivisione della relazione di valutazione della parte II
- "Repository" per i documenti necessari ai fini di input su parte I e valutazione parte II da parte del Comitato Etico

# OsSC e potenziali sviluppi

- CoI/DoI componenti del Comitato Etico
- Anagrafiche puramente nazionali
- Informazioni di dettaglio su base nazionale (anche al pubblico) potenzialmente non presenti nel portale
- Reportistica e monitoraggio anche in supporto alle Regioni.
- … … … … … … … … … … ???

# Voluntary Harmonization Procedure (VHP)

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## Before May 2004

Different **processes and requirements** for clinical trial authorisations in each Member States…

… resulted in **delays and complications** detrimental to effective conduct of clinical trials in the EU.

## Directive 2001/20/EC

First step to harmonise **processes and requirements** for clinical trial authorisations.

Implementation **1 May 2004**.

**Concerns expressed** soon after its implementation.

## Regulation (EU) 536/2014

Published **on 27 May 2014.**

**Application 6 months after** confirmation published in the OJ of **full functionality of EU portal and EU database**, in any event **not earlier than 28 May 2016.**

**Transitional arrangements.**

# Direttiva 2001/20/CE S.M.I.

# Direttiva 2001/20/CE S.M.I.

- Differenti Valutazioni
- Differenti tempistiche
- Differenti decisioni

Necessità di armonizzazione attraverso emendamenti sostanziali

# Regolamento 536/2014/CE

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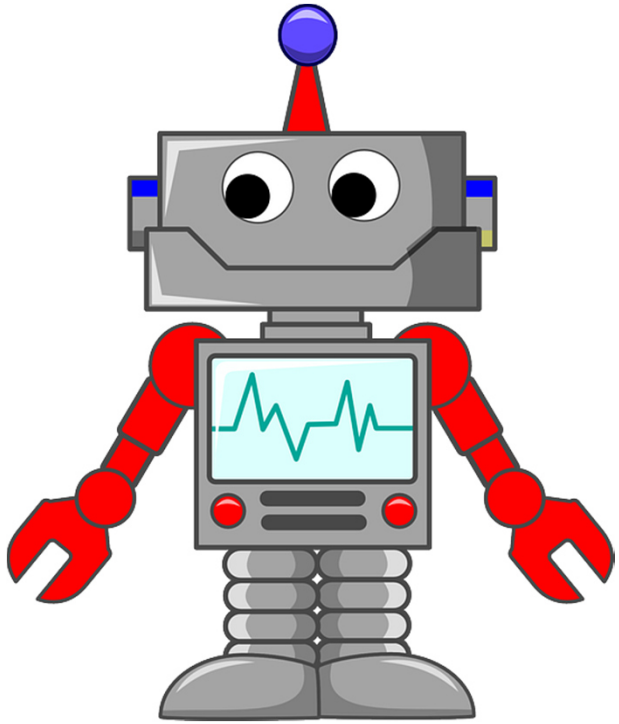
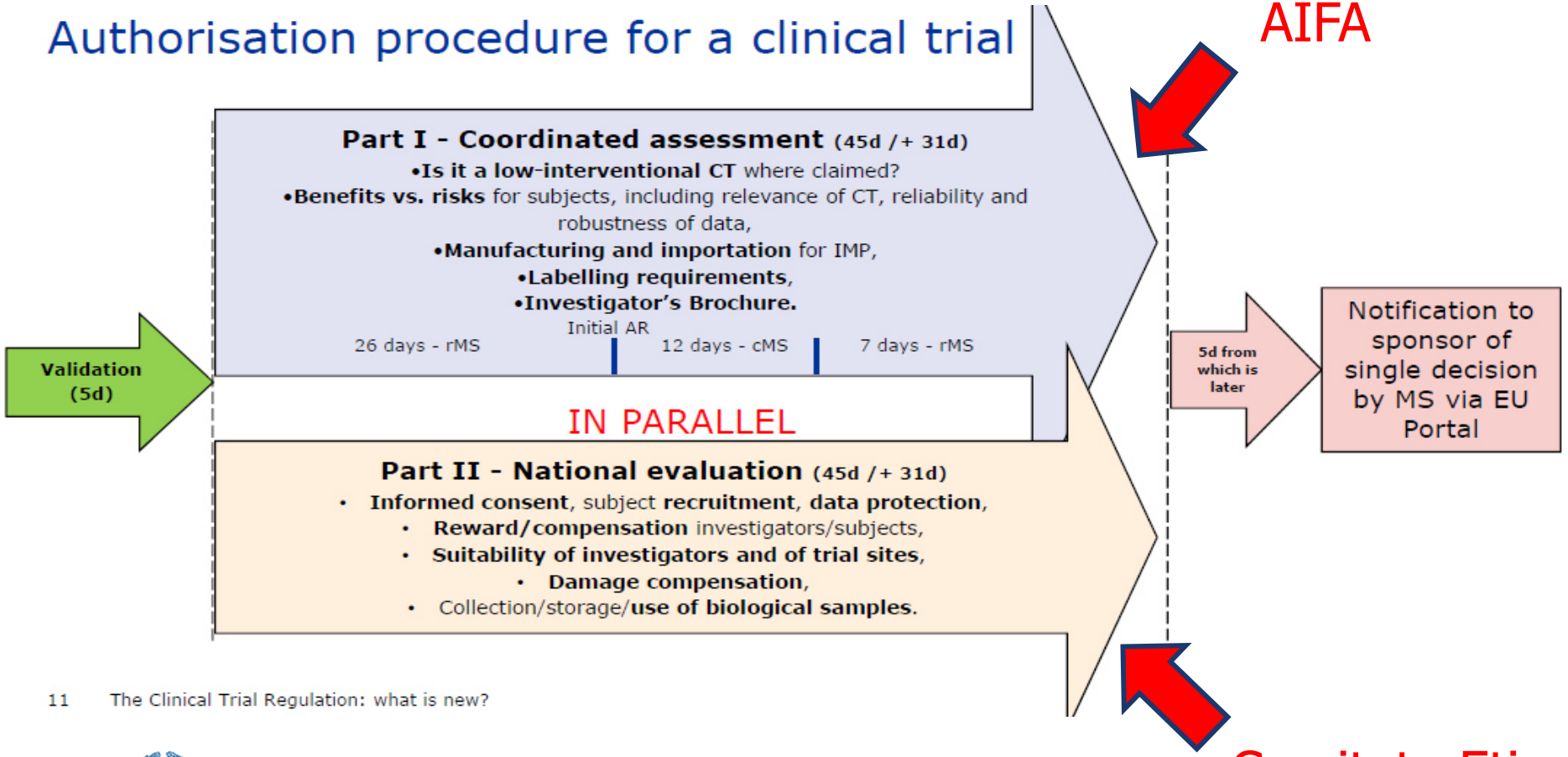
# Regolamento 536/2014/CE



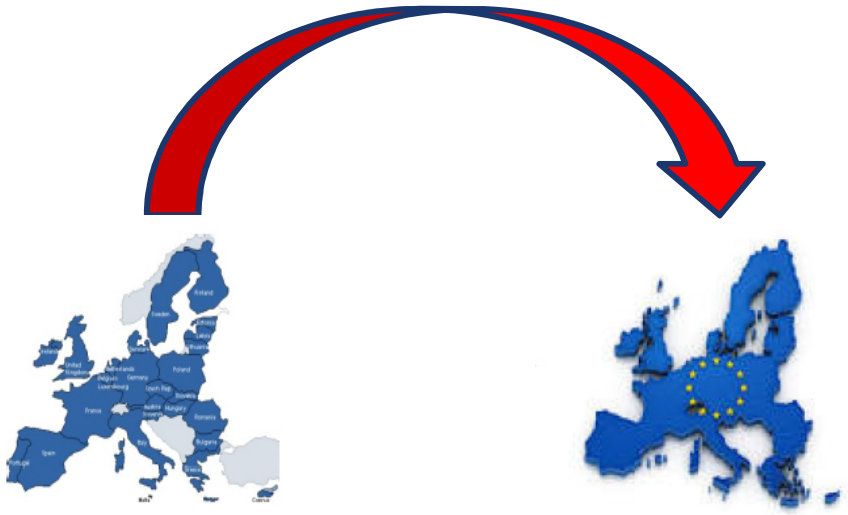
- Valutazione uniforme
- Tempistica definita
- Decisione armonizzata

Razionalizzazione delle risorse per le Autorità competenti nazionali (NCA) e riduzione dei costi per le Companies

# Adeguamento al Nuovo regolamento



# How Italy supports the transition to the new regulation



2001/20/CE 536/2014

- VHP
- Pilot projects
- EU Portal
- National IT system
- Training

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## Voluntary Harmonization Procedure

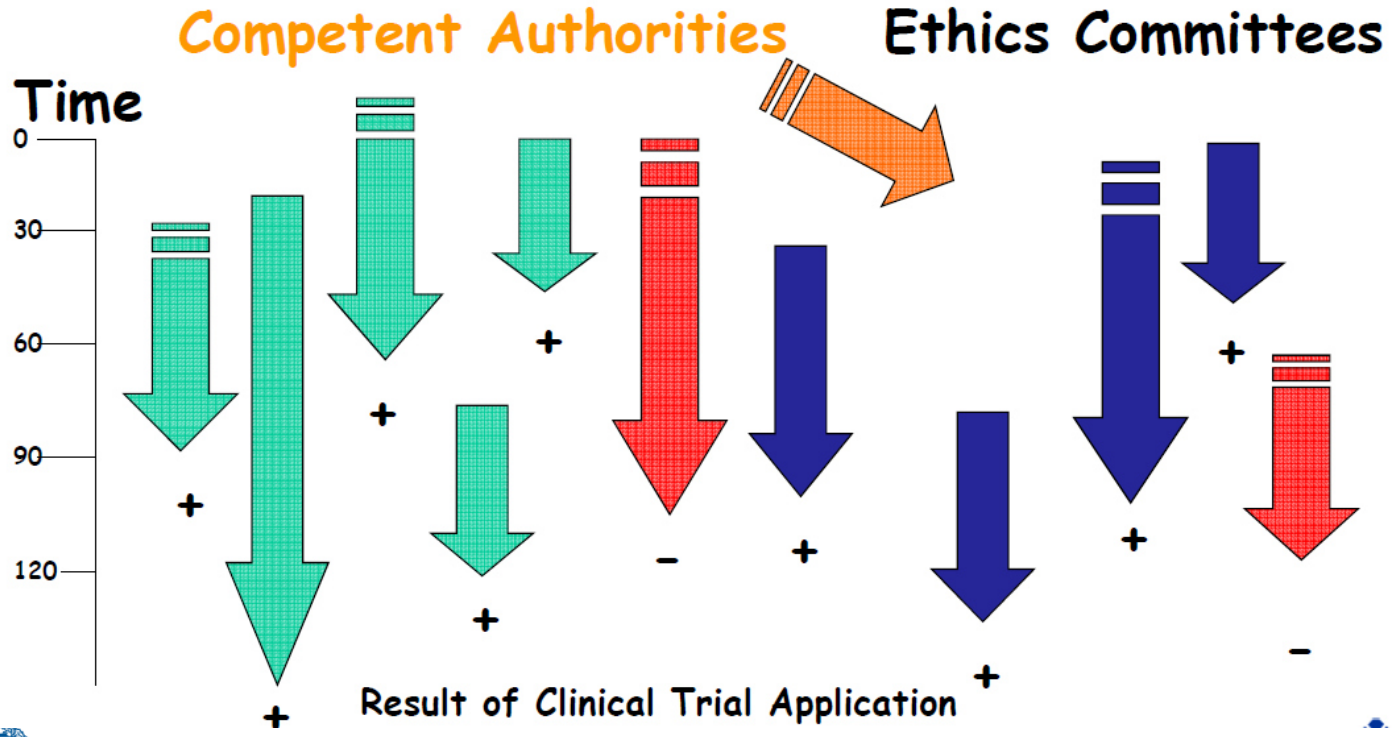
2001/20/CE

536/2014

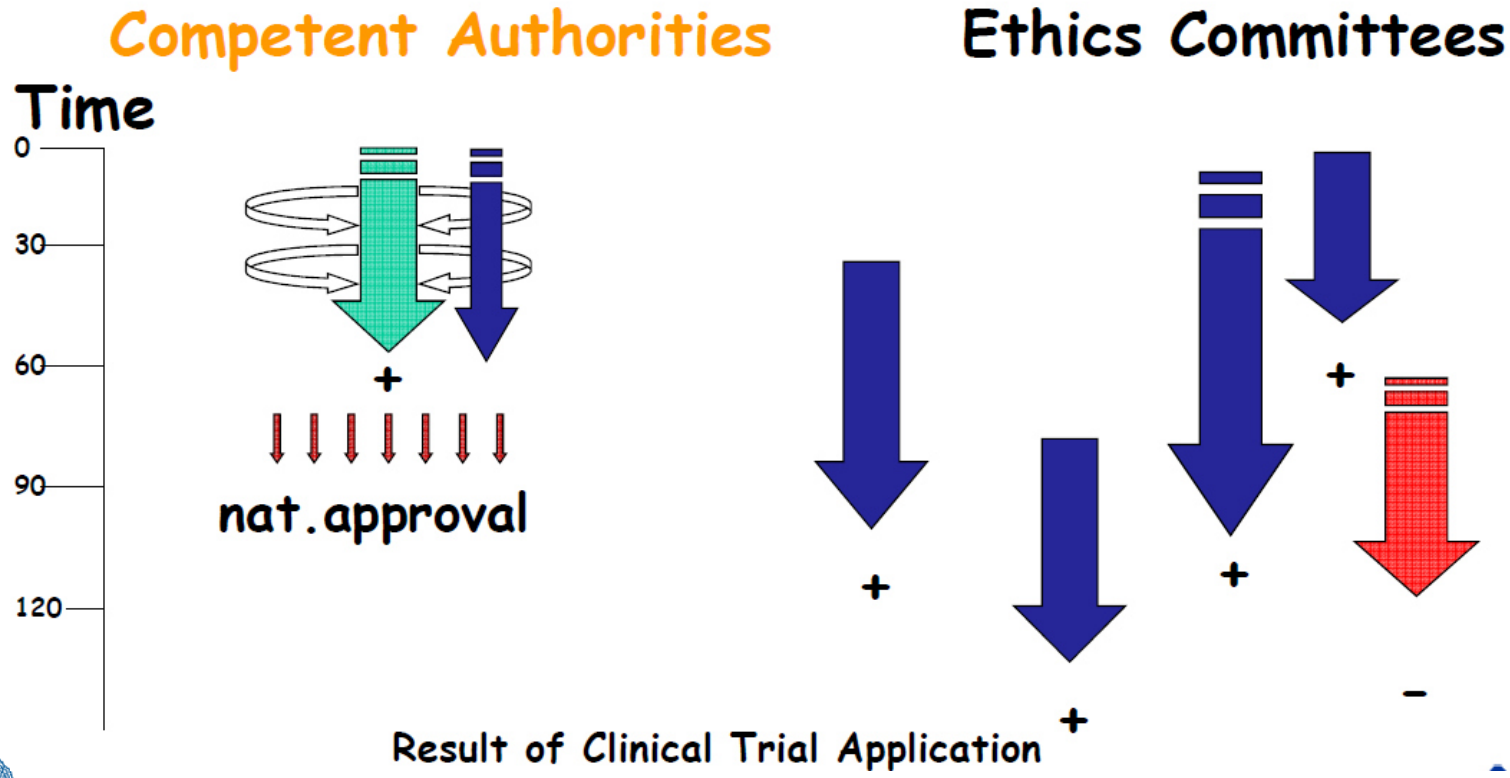
# The Voluntary Harmonisation Procedure

La VHP è una procedura applicabile su base volontaria per gli studi clinici di fase I-IV multicentrici che sono svolti in più Stati Membri dell'UE e che permette la valutazione/autorizzazione coordinata dei clinical trials in un'unica soluzione contemporanea per tutti gli stati coinvolti nella sperimentazione.

# Approvazione delle richieste di autorizzazione alla Sperimentazione clinica: Procedure nazionale



# Approvazione delle richieste di autorizzazione alla Sperimentazione clinica: VHP



# The Voluntary Harmonisation Procedure

- Circolazione di documenti in formato elettronico tramite una casella di posta elettronica accessibile a tutte le NCA che partecipano al progetto.
- Lista di documenti stabilita e armonizzata per tutte le procedure.
- Tempistica per la valutazione scientifica e etica dello studio definita e rigorosa.
- Unica valutazione scientifica a cui partecipano tutte le NCAs degli stati membri coinvolti nella sperimentazione.
- Decisione finale sulla possibile approvazione della sperimentazione a livello nazionale armonizzata.

# Circolazione dei documenti

L'Application tramite VHP viene richiesta dall'Applicant al VHP-Coordinator, che inoltra la richiesta alle NCAs degli Stati Membri coinvolti nella sperimentazione. La richiesta e tutte le notifiche vengono fatte circolare attraverso una casella di posta elettronica alla quale accedono le NCAs.

Nessuna comunicazione tra Sponsor/Applicant e NCAs

# The Voluntary Harmonisation Procedure

- Circolazione di documenti in formato elettronico tramite una casella di posta elettronica accessibile a tutte le NCA che partecipano al progetto.
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- Unica valutazione scientifica a cui partecipano tutte le NCAs degli stati membri coinvolti nella sperimentazione.
- Decisione finale sulla possibile approvazione della sperimentazione a livello nazionale armonizzata.

# Lista dei documenti predefinita

- Informazioni generali (Cover letter, CTA form)
- IMPD e documenti associati
- Investigator's Brochure
- Study Protocol
- Additional information (Scientific advices, PIP etc.)

Documentazione inviata dall'Applicant e fatta circolare dal VHP-C tramite Eudralink

# The Voluntary Harmonisation Procedure

- Circolazione di documenti in formato elettronico tramite una casella di posta elettronica accessibile a tutte le NCA che partecipano al progetto.
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- Unica valutazione scientifica a cui partecipano tutte le NCAs degli stati membri coinvolti nella sperimentazione.
- Decisione finale sulla possibile approvazione della sperimentazione a livello nazionale armonizzata.

# The Voluntary Harmonisation Procedure

## timelines for VHP

VHP Application Date: **01.10.2015** Date of Start VHP: **08.10.2015**

| type of deadline | due on | Day |
|---|---|---|
| Confirmation of receipt to Sponsor | 03.10.2015 | -5 |
| Date informing NCA on VHP/VHP-Dossier location in VHP area | 03.10.2015 | -5 |
| Final acknowledgement of receipt to Sponsor | 08.10.2015 | 0 |
| DAR/GNAs to be stored in VHP-area/VHP-Database by Ref.-NCA | 28.10.2015 | 20 |
| Statement on ASR/GNAs by P-NCAs and additional GNA to be entered in VHP-DB | 02.11.2015 | 25 |
| Date of consolidated List of GNAs by Ref-NCA in VHP-Database due by | 05.11.2015 | 28 |
| Date acceptance P-NCA of consolidated list of GNA | 06.11.2015 | 29 |
| TC on GNA before | 07.11.2015 | 30 |
| Info of Sponsor on GNAs by | 09.11.2015 | 32 |
| Response on GNA by sponor due by | 19.11.2015 | 42 |
| Assessment of response by Ref.-NCA in VHP-area / VHP-Database by | 26.11.2015 | 49 |
| Response of P-NCAs on assessment by Ref.-NCA in VHP-Database by | 03.12.2015 | 56 |
| Final ASR by Ref-NCA to be stored in VHP-area by | 04.12.2015 | 57 |
| TC on unsolved GNA before | 05.12.2015 | 58 |
| End of VHP / final info to Sponsor | 07.12.2015 | 60 |
| National applications by Sponsor | 27.12.2015 | 80 |
| National approvals by NCA | 06.01.2016 | 90 |

Validazione e candidature
(5 giorni)

Valutazione Tecnica
(60 giorni)

Approvazione Nazionale
(10 giorni)

# The Voluntary Harmonisation Procedure

- Circolazione di documenti in formato elettronico tramite una casella di posta elettronica accessibile a tutte le NCA che partecipano al progetto.
- Lista di documenti stabilita e armonizzata per tutte le procedure.
- Tempistica per la valutazione scientifica e etica dello studio definita e rigorosa.
- Unica valutazione scientifica a cui partecipano tutte le NCAs degli stati membri coinvolti nella sperimentazione.
- Decisione finale sulla possibile approvazione della sperimentazione a livello nazionale armonizzata.

# Unica discussione scientifica

- La valutazione tecnico/scientifica viene eseguita da una NCA (Reference-NCA) coinvolta nella sperimentazione che si occuperà di redigere un documento (Assessment Report) fruibile per tutte le altre NCA (Participant-NCAs).
- Tale valutazione è di solito accompagnata da una lista di obiezioni che se non risolte dall'Applicant precludono l'autorizzazione dello studio (Grounds for non acceptance – GNA).
- Le altre P-NCAs partecipano alla discussione tecnico/scientifica fornendo i propri commenti alla Ref-NCA e aggiungendo eventuali GNAs.
- La decisione sulla lista finale delle GNA da inviare all'Applicant rimane compito della Ref-NCA che opererà nell'ottica dell'armonizzazione tra le NCAs.

# The Voluntary Harmonisation Procedure

- Circolazione di documenti in formato elettronico tramite una casella di posta elettronica accessibile a tutte le NCA che partecipano al progetto.
- Lista di documenti stabilita e armonizzata per tutte le procedure.
- Tempistica per la valutazione scientifica e etica dello studio definita e rigorosa.
- Unica valutazione scientifica a cui partecipano tutte le NCAs degli stati membri coinvolti nella sperimentazione.
- Decisione finale sulla possibile approvazione della sperimentazione a livello nazionale armonizzata.

# Unica decisione valida per tutti gli Stati Membri coinvolti

- La valutazione di uno studio clinico in VHP può avere 3 esiti diversi:
- *VHP approvable*
- *VHP approvable with conditions*
- *VHP to be rejected*

Lo stesso esito sarà applicabile a tutti gli Stati membri coinvolti nella VHP

# Valutazione scientifica – Parte I

- Una delle NCAs coinvolte nella sperimentazione (Reference-NCA) si occuperà di fornire un assessment report dettagliato dello studio completo di eventuali obiezioni che se non risolte dall'Applicant precludono l'approvazione dello studio (Grounds for non acceptance – GNA) – Day 20.
- Le altre NCAs coinvolte nella sperimentazione (Participant-NCAs) potranno commentare le GNAs sollevate dalla Ref-NCA ed eventualmente aggiungerne di ulteriori – Day 25.
- La Ref-NCA produrrà una lista di GNAs consolidata che terrà conto dei commenti delle altre NCA – Day 28.
- Tale lista dovrà essere accettata dalle P-NCAs – Day 29.
- Tale lista di GNAs verrà inviata all'Applicant dal VHP-Coordinator – Day 30/32.

# Valutazione scientifica – Parte II

- L'Applicant ha 10 giorni di tempo per redigere un documento con le risposte alle GNA sollevate nella I fase. Una volta pronto il documento viene inviato al VHP-Coordinator che provvederà a inviarlo a tutte le NCAs coinvolte nella sperimentazione – Day 32-42.
- La Ref-NCA entro 7 giorni farà circolare un Assessment report completo delle risposte dell'Applicant e dei commenti a tali risposte, dichiarando se le GNA sono state risolte o meno e fornendo un parere conclusivo sulla sperimentazione – Day 49.
- Le altre P-NCAs entro i successivi 7 giorni hanno la facoltà di fornire i propri commenti alla valutazione della Ref-NCA – Day 56.
- La Ref-NCA raccoglie tutti i commenti e fornisce la decisione finale sulla sperimentazione (Day 57) che viene inviata all'Applicant dal VHP-Coordinator (Day 58/60).

# Esito della valutazione

Feedback delle altre P-NCAs al parere della RefNCA

Positivo: la decisione della Ref-NCA è condivisa

Negativo: la decisione della Ref-NCA non è condivisa

Conclusion of the VHP

Divergent position

# Conclusione della VHP

| | | |
|---|---|---|
| VHP approvable | → | Autorizzazione della sperimentazione a livello nazionale |
| VHP approvable with conditions | → | Parere positivo sulla sperimentazione solo dopo aver verificato l'effettiva implementazione |
| VHP to be Rejected | → | Diniego dell'autorizzazione anche a livello nazionale |

# Divergent Position

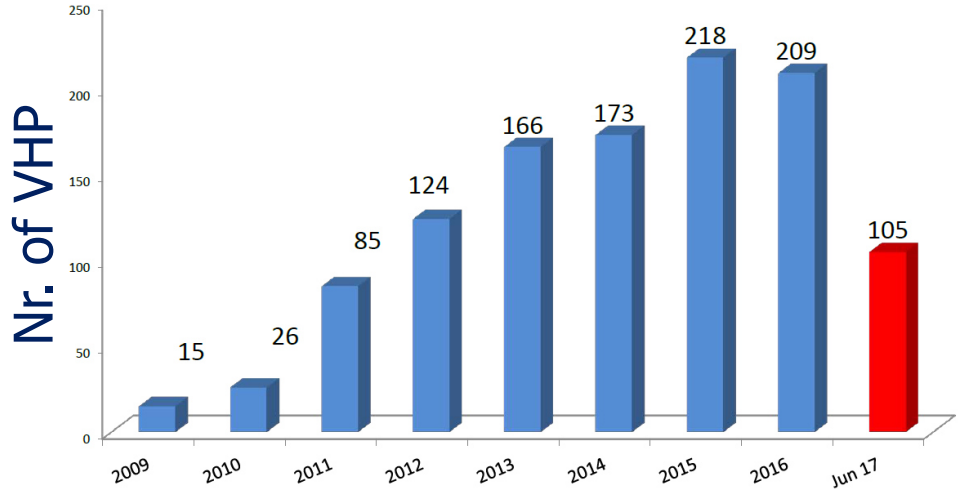
Se non viene raggiunta una posizione condivisa tra le NCAs l'esito della VHP potrà essere differente tra le varie NCAs coinvolte nella sperimentazione

Decisione diversa tra gli Stati Membri

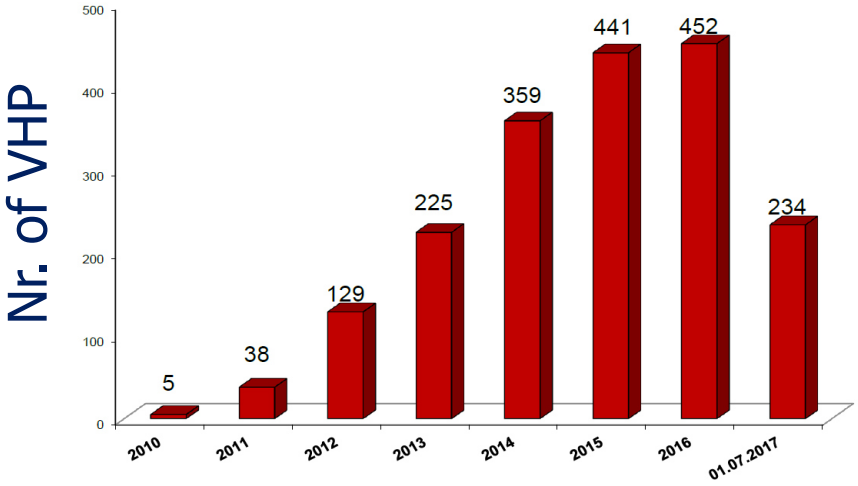
Diversità nei documenti

# Increasing Numbers of VHP applications

## Initial submission




## Substantial Amendments

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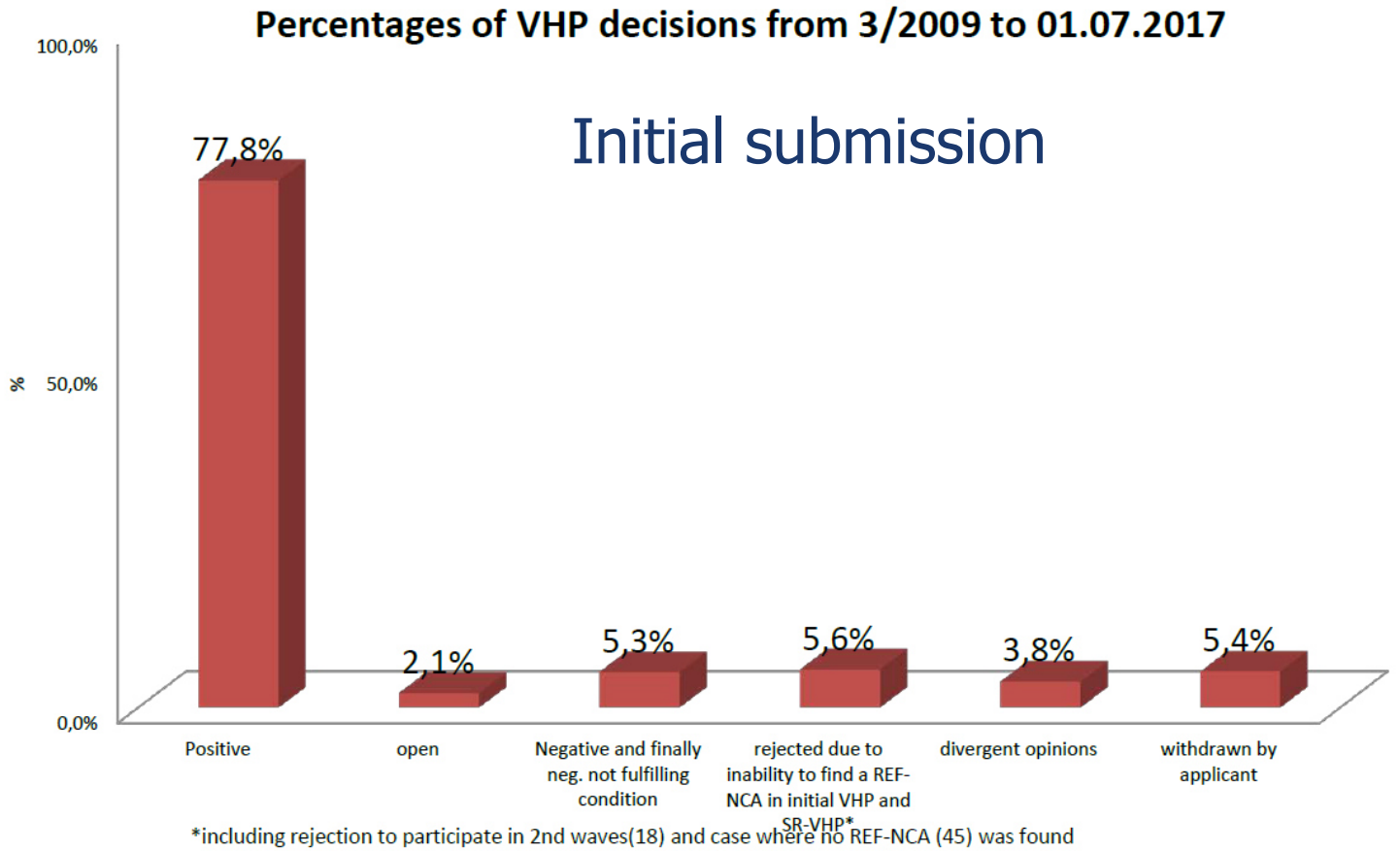
# Outcomes of VHP Applications




*including rejection to participate in 2nd waves(18) and case where no REF-NCA (45) was found

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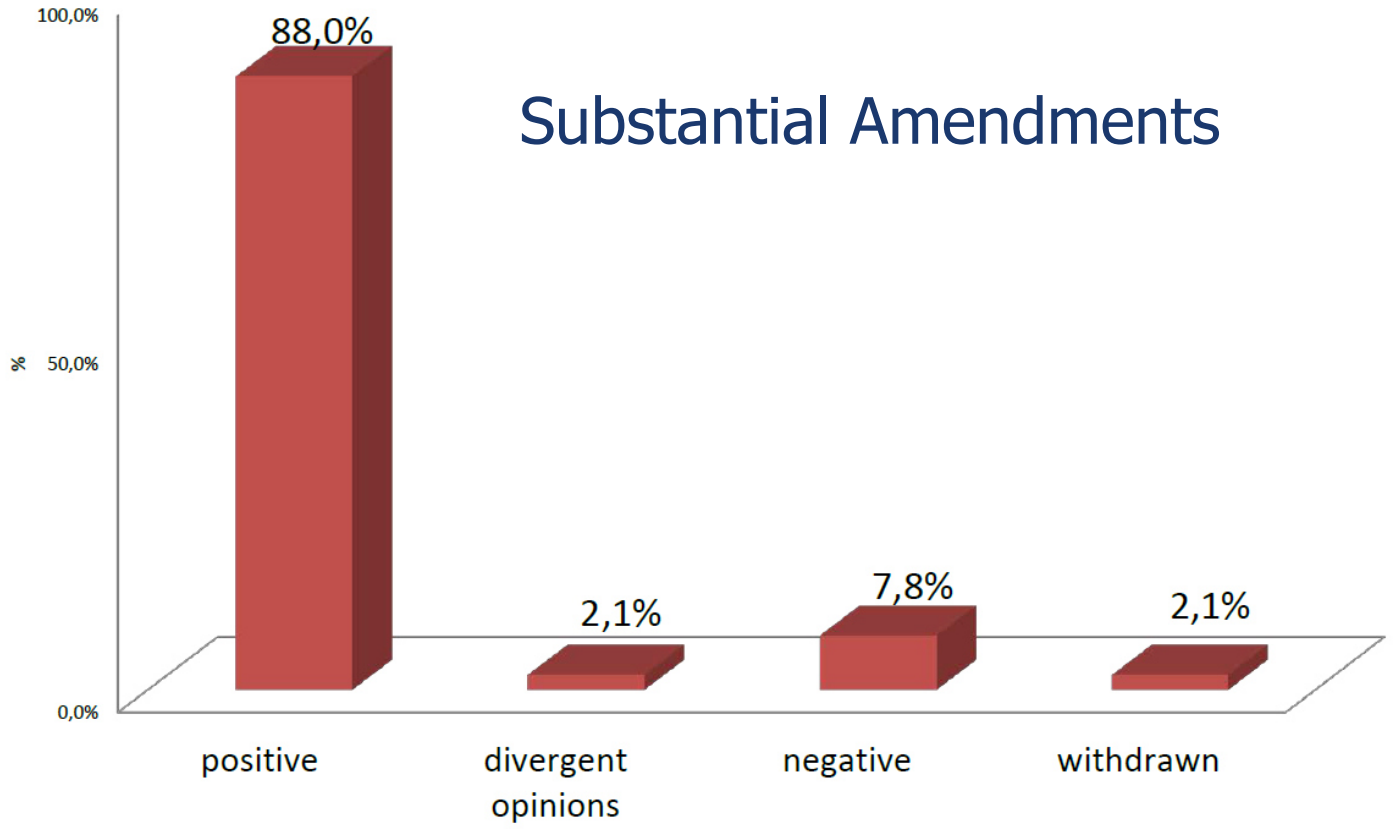
# Outcomes of VHP Applications

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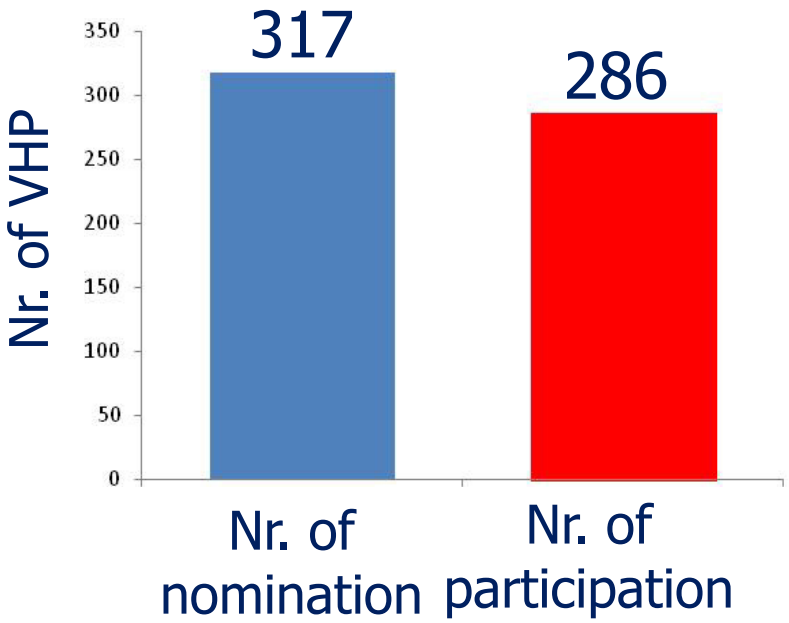
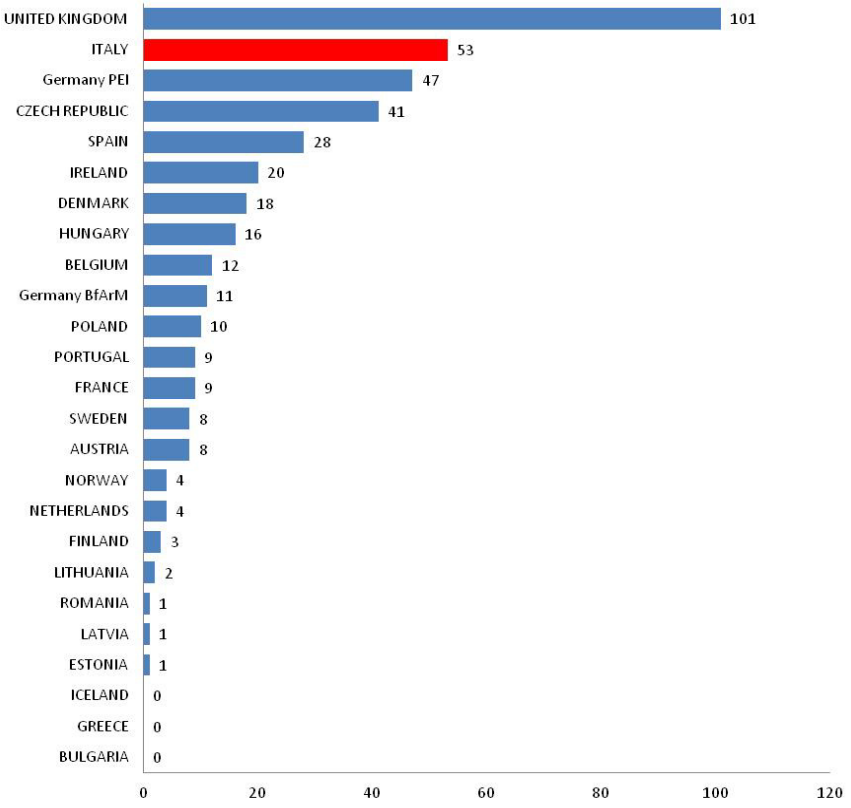
# The role of Italy in VHP

- AIFA has been nominated National Competent Authority for the authorization of CTA only in 2013
- Due to the limited resources the participation of Italy in VHP has been poor until 2015
- Starting from 2015 AIFA implemented the resources and actively participates to the VHP.

# IT involvement in VHP (2015-2017)

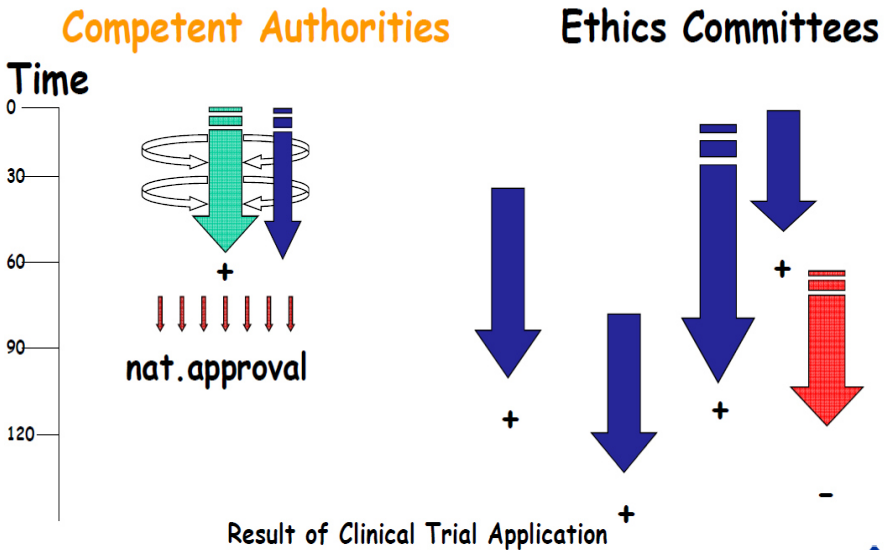



Nr. of VHP as Ref-NCA



# Recent Progresses in VHP
# Involvment of Ethical committes:
# VHP Plus

**EU Voluntary Harmonisation Procedure (VHP) for multinational Clinical Trials**




VHP-plus is a VHP involving Ethics Committees in the assessment of benefit/risk, IB and protocol in some Member States

# Coordinated assessment AIFA and EC:
## *The Pilot Project*

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# Ethics committees in Italy

Currently in Italy there are about 100 different ethics committees distributed in different regions according to the number of inhabitants.


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# Authorization of CT in Italy

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- IMPD
- IB
- Protocol

Coordinator EC

- IMPD
- IB
- Protocol
- ICF
- Administrative documents

Collaborators EC

- ICF
- Administrative documents
- "Local feasibility"

- Different conclusions
- Different timelines
- Delay in the start of the CT

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# The pilot project

Objective:

- To harmonize evaluation, timelines and national authorization of the clinical studies submitted via VHP

Endpoints:

- To grant the national authorization of CT with the EC opinion within the VHP timelines
- To test the "feasibility" of a harmonized procedure in view of the new CTR
- To take essential information for the re-organization of EC in Italy

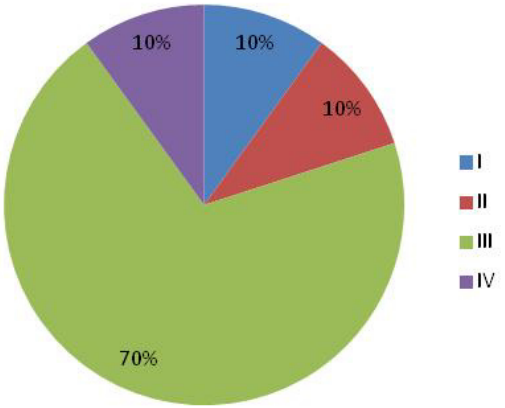
# The pilot project

- If a Sponsor wants to adhere to the project, he communicates the CEC to AIFA and agrees to share the VHP documentation with the CEC.
- AIFA communicates the Sponsor request to the CEC and then starts the coordinated assessment with CEC.
- The CEC agrees to be compliant with the VHP timelines. If CEC does not respect the timeline, the coordinated assessment will be closed and a communication will be sent to the sponsor.
- AIFA goes on with the VHP without the CEC, who will provide his evaluation during the national step.

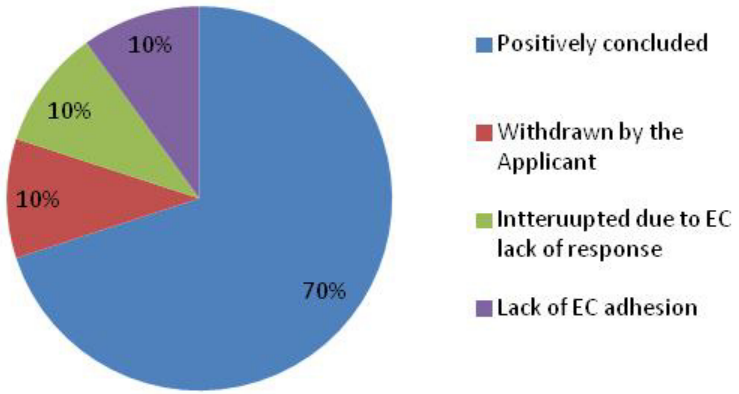
# Preliminary results of the pilot project (2016 – 2017)

The project started in May 2016 and 10 procedures have been assessed with EC so far

Distribution of the phases




Outcome of the procedures assessed in the VHP phase



# Preliminary results of the pilot project (2016 – 2017)

## Outcome of the VHP procedures assessed within the pilot project in the national step

| VHP | National Application | AIFA Authorisation | EC Authorisation |
|---|---|---|---|
| VHP916 | 30/08/2016 | 01/09/2016 | 21/12/2016 |
| VHP965 | 29/12/2016 | 05/01/2017 | 17/01/2017 |
| VHP1014 | 27/04/2017 | 09/05/2017 | 19/05/2017 |
| VHP1038 | 12/04/2017 | 09/05/2017 | Ongoing |

# Contribution of the EC to the pilot project

## Comments

EC sent Comments
in 4/7 procedures

Number of comments:
EC = 7
AIFA = 37

# National IT system: OsSC



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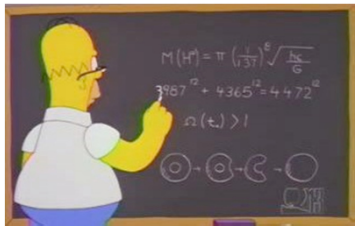
# EU Network Training



The CTFG in collaboration with EMA (EU Network Training Centre) and single NCA organizes training on topics related to the new regulation

- Clinical Trials Regulation Training (EMA – London, 3-4 March 2016)
- Clinical Trials Safety training & workshop (HPRA – Dublin, 28-29 Sept 2016)
- Clinical trials workshop on clinical assessment (AIFA – Rome, 21-22 Nov 2016)
- First in Human trials training (FAMHP - Q1 2017)
- Quality and safety training for assessors (Prague 23-24 and 25-26 Oct 2017)

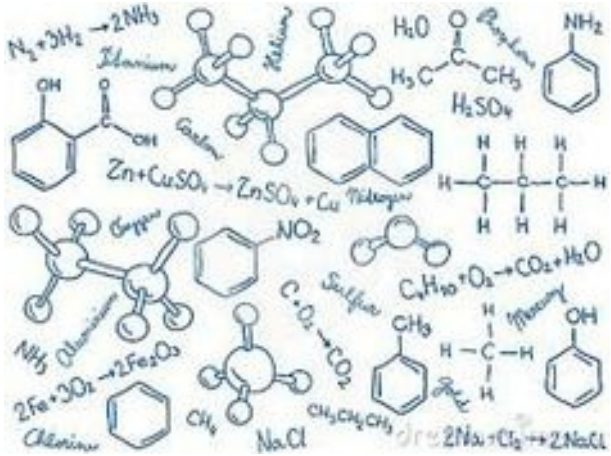
# Conclusions: progress in national implementation so far

- VHP
- Pilot projects
- EU Portal
- National IT system
- Training

# La vision di AIFA

# Ringraziamenti

- AIFA
- Dott. M. Sarra
- Organizzatori Master



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