NUEVAS EXIGENCIAS CIENTÍFICAS Y REGULATORIAS EN LA INVESTIGACIÓN BIOMÉDICA: VISIÓN DE LOS PROMOTORES Y DE LOS CENTROS.

4 Abril 2019

Dña. Silvia Graell (Amgen)
Dña. Elvira García Jordà (Pfizer)

- Situación actual de la investigación Clínica en España
- Estrategias a seguir como país para atraer más investigación
- Exigencias de los centros para ser considerados de excelencia
- Innovación: nuevas exigencias en camino
- Conclusiones

1. Situación de la Investigación Clínica en España

Situación actual de la investigación clínica

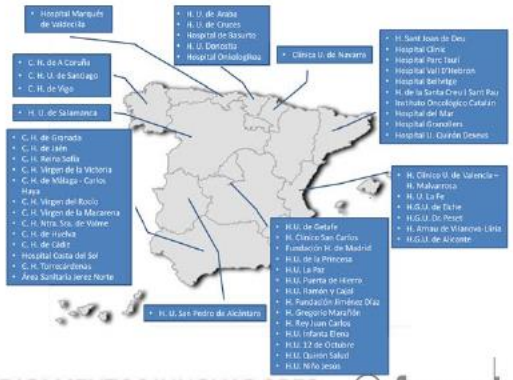
45 Laboratorios

Investigación clínica independiente

- Grupo Español de Investigación en Cáncer de Mama (GEICAM)
- Grupo Español de Tratamiento de Tumores Digestivos
- Grupo Académico de Investigación de Referencia en Cáncer de Mama
- Grupo Español de Cáncer de Pulmón (GECP)
- Grupo Quirónsalud
- Clínica Universidad de Navarra (CUN)

13 CCAA

55 centros adheridos



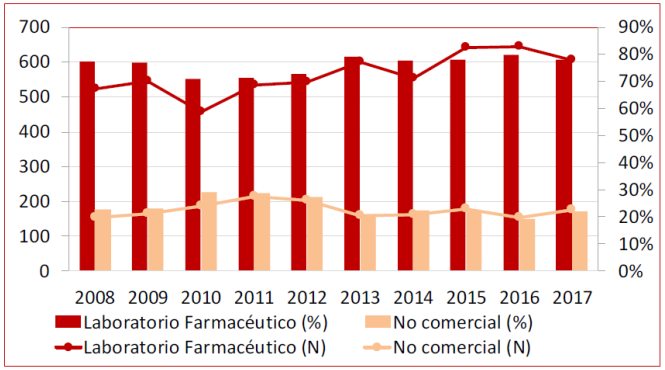
Datos y Análisis 25ª Publicación BDMetrics
5 de noviembre de 2018

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

Situación actual de la investigación clínica

Durante el periodo 2005-2017 la AEMPS ha autorizado 9.267 ensayos clínicos, cerca del 78% de estos fueron autorizados a Laboratorios Farmacéuticos.

Distribución del porcentaje (eje derecho) y del número absoluto (eje izquierdo) de los ensayos clínicos autorizados por tipo de promotor



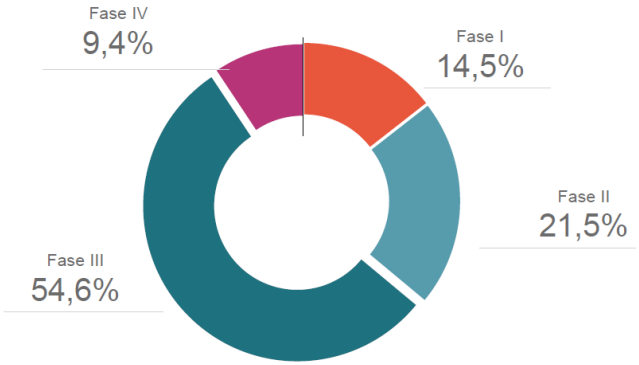
Fuente memorias de la AEMPS

Cerca del **42% de los ensayos clínicos autorizados por la AEMPS** a los **Laboratorios Farmacéuticos** en el periodo **2005-2017** se encuentran en la BDMetrics del proyecto BEST. Adicionalmente, en ese mismo periodo BDMetrics contiene **167 ensayos** de **Grupos de Investigación Independiente autorizados por la AEMPS**.

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total 2005-17
Nº EECC autorizados por la AEMPS (1)	675	707	643	748	745	759	714	818	799	780	9.267
% EECC en los que el promotor es un Laboratorio Farmacéutico (1)	77%	77%	71%	71%	73%	79%	78%	78%	81%	78%	78%
Nº EECC autorizados por la AEMPS a Laboratorios Farmacéuticos	523	544	457	534	542	601	554	641	645	605	7.225
Nº EECC en BDMetrics con fecha de autorización de la AEMPS en el año (2)	244	263	225	218	233	260	205	250	228	203	2.999
% EECC en BDMetrics/EECC de la industria autorizados por la AEMPS	47%	48%	49%	41%	43%	43%	37%	39%	35%	34%	42%

(1) Fuente memorias de la AEMPS
(2) Fuente BDMetrics del proyecto BEST

En 2017 se invirtieron **662 millones de euros** en **investigación clínica**, de los cuales **un 36% se destinaron a fases tempranas (fases I y II), tres puntos más que en 2016.**



Fuente: Farmaindustria

España – 1er país adoptando la Regulación Europea

EU REGULATION No 536/2014


Diario Oficial de la Unión Europea

L 158

Legislación

27 de mayo 2014

Reglamento (UE) nº 536/2014 del Parlamento Europeo y del Consejo, de 16 de abril de 2014, sobre los ensayos clínicos de uso humano, y por el

RD 1090/2015


Cinco Días

20 Noviembre, 2017

Innovación en los laboratorios

La industria farmacéutica convierte a España en una potencia en ensayos clínicos

La anticipación a la normativa europea es bien recibida por los laboratorios

En el último año crece un 18% la I+D de las compañías con hospitales

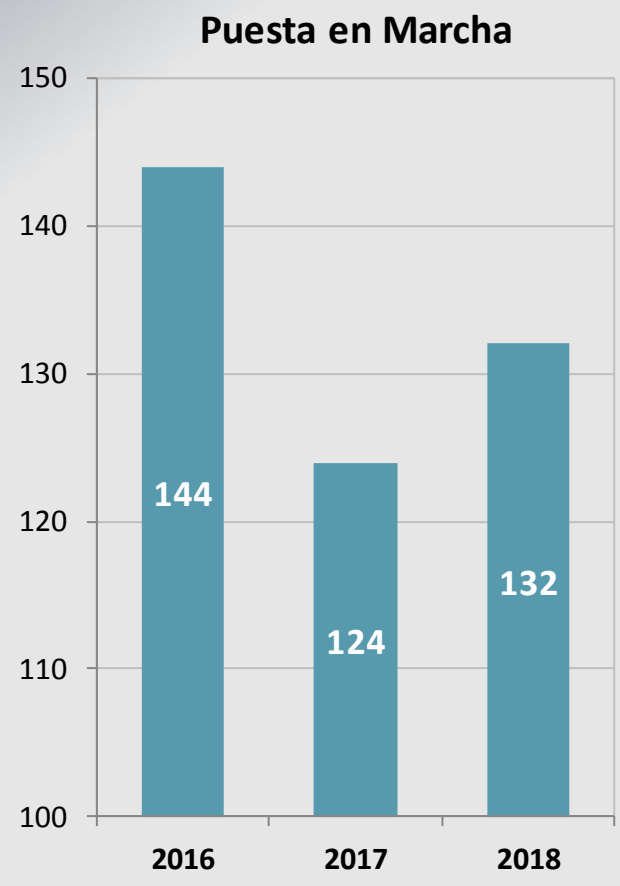
La investigación con pacientes de la industria

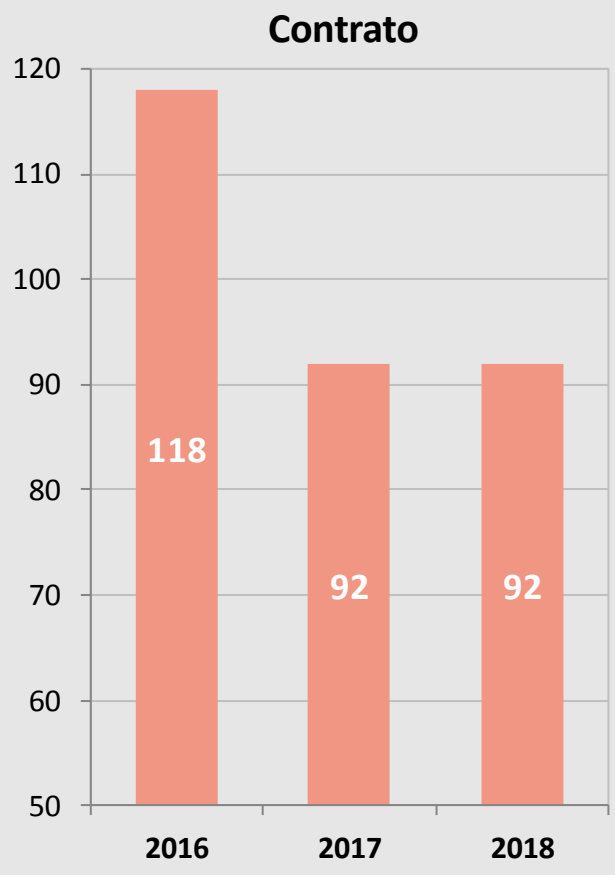
Estudios clínicos en España Número de ensayos autorizados

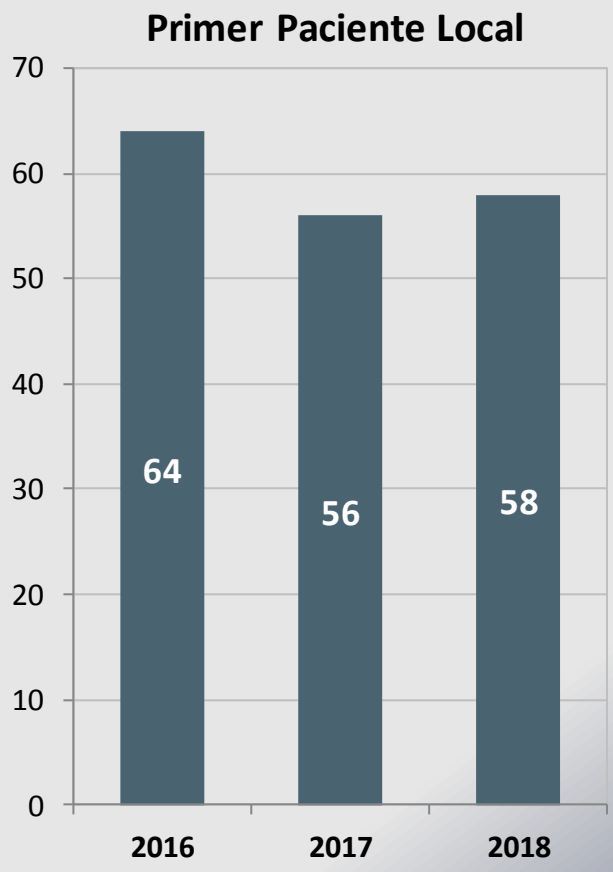
Evolución del gasto en I+D Miles de millones de euros

Entorno Regulatorio - atractivo

Análisis de los tres primeros años del RD 1090/2015





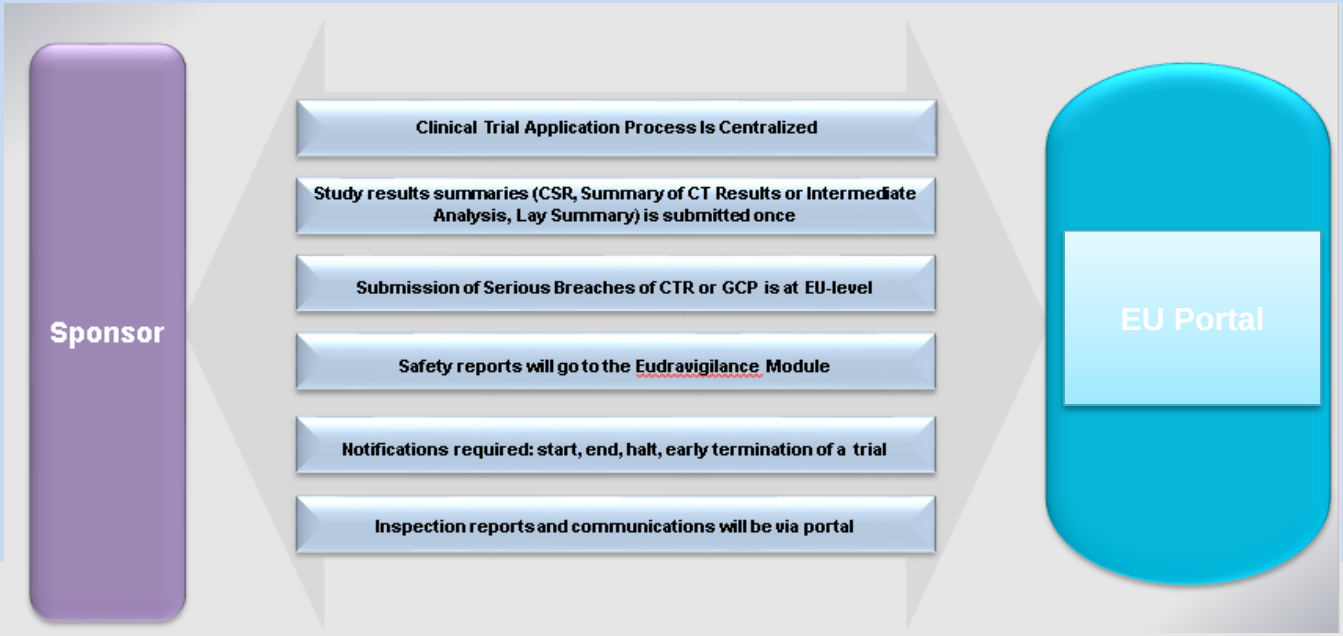


•Datos del Avance de la 26ª Publicación

(I)Aumento de tiempo respecto a la 25ª publicación (40 d) , debido a actualizaciones de ensayos y nueva información disponible

Entorno Regulatorio – EU CTR (Q4 2020)

- Introduces an **EU Portal and Database** through which submissions/ documents/communications must flow
- **Streamlines the procedures** to assess and authorise new clinical studies
- Introduces additional **transparency provisions**
- Introduces a **lighter regulatory regime** for trials conducted with medicines which are already authorised ("Low Intervention Clinical Trials")



2. Estrategia como país para atraer más investigación clínica

Estrategia →
Exigencias del promotor para atraer más Investigación Clínica

Scientific talent Patients

- Scientific Experts & experience in Clinical Trials
- Provide medical/scientific insight to study design
- Attract (↑) Early Phase studies
- Sufficient patient population

Improve Competitiveness

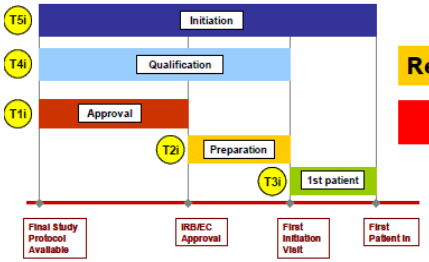
- High Enrolment predictability
- Enrollment ratio (patients/ site). First Patient In (FPI)
- Competitive Start-up timelines
- High Quality data/Data Entry
- Cost competitiveness

Innovation in Clinical Trials

- Risk Based Monitoring
- Innovative and Adaptive Study Design
- Digitalization

Estrategia → ¿suficientemente competitivos ?

BI: Ranking de España resto países



Resto de países

España

Se muestra el **puesto** que ocupa **España** dentro de cada etapa.

El número 1 es el país que menos tarda en esa etapa.

Approval	Preparation	1st patient	Qualification	Initiation
1	1	1	1	1
2	2	2	2	2
3	3	3	3	3
4	4	4	4	4
5	5	5	5	5
6	6	6	6	6
7	7	7	7	7
8	8	8	8	8
9	9	9	9	9
10	10	10	10	10
11	11	11	11	11
12	12	12	12	12
13	13	13	13	13
14	14	14	14	14
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16	16	16	16	16
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18	18	18	18	18
19	19	19	19	19
20	20	20	20	20
21	21	21	21	21
22	22	22	22	22
23	23	23	23	23
24	24	24	24	24
25	25	25	25	25
26	26	26	26	26
27	27	27	27	27
28	28	28	28	28
29	29	29	29	29
30				30
				31

3. Exigencias a los centros para ser considerados de excelencia

Agilidad en la puesta en marcha

Primer centro iniciado

- ✓ Interlocutor válido
- ✓ Tramitación de la documentación ensayo
- ✓ Existencia de Contratos Marco

Primer paciente reclutado

- ✓ Simplificación de la memoria económica
- ✓ Reducción tiempo firma del contrato

Recursos e Infraestructura

Nivel Científico del investigador

Personal de soporte a investigación

Colaboración otros Servicios

Calidad de los datos

Acceso al CRA a EMRs

Instalaciones adecuadas

Capacidad de Reclutamiento

- Rapidez en reclutar y fiabilidad en el cumplimiento de compromisos

- Métricas cualitativas y cuantitativas de actividad:

  - número de ensayos clínicos
  - pacientes reclutados
  - tiempo de puesta en marcha
  - tiempo de entrada del 1r paciente
  - tiempo de entrada de datos al CRD
  - resultados en inspecciones y auditorias

- Medios para incrementar el reclutamiento:

  - Plataformas digitales: TriNetX/Insite
  - Referral Networks- centros de atención primaria
  - Publicitar internamente los EECCs de un centro
  - Materiales de soporte y vendors externos
  - Asociaciones de **pacientes**

Servicio de Farmacia Hospitalaria

Gestión Clínica

Profesionalización

Financiación

Integridad de los datos

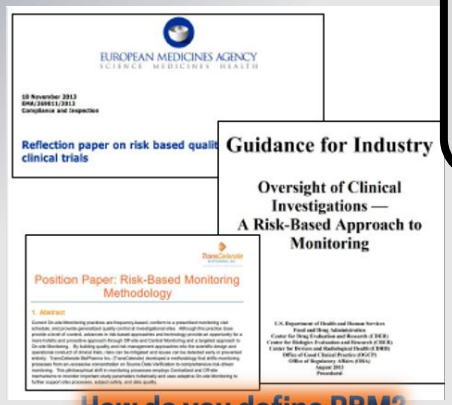
Garantizar la seguridad del paciente

Instalaciones certificadas

Estandarización de procesos

4. Innovación: Nuevas exigencias en camino

Monitorización Basada en el Riesgo vs modelo tradicional



2013 - FDA recognizes the need for more efficient, effective, targeted monitoring
Overall focus is on planning trial monitoring through documented risk-assessment

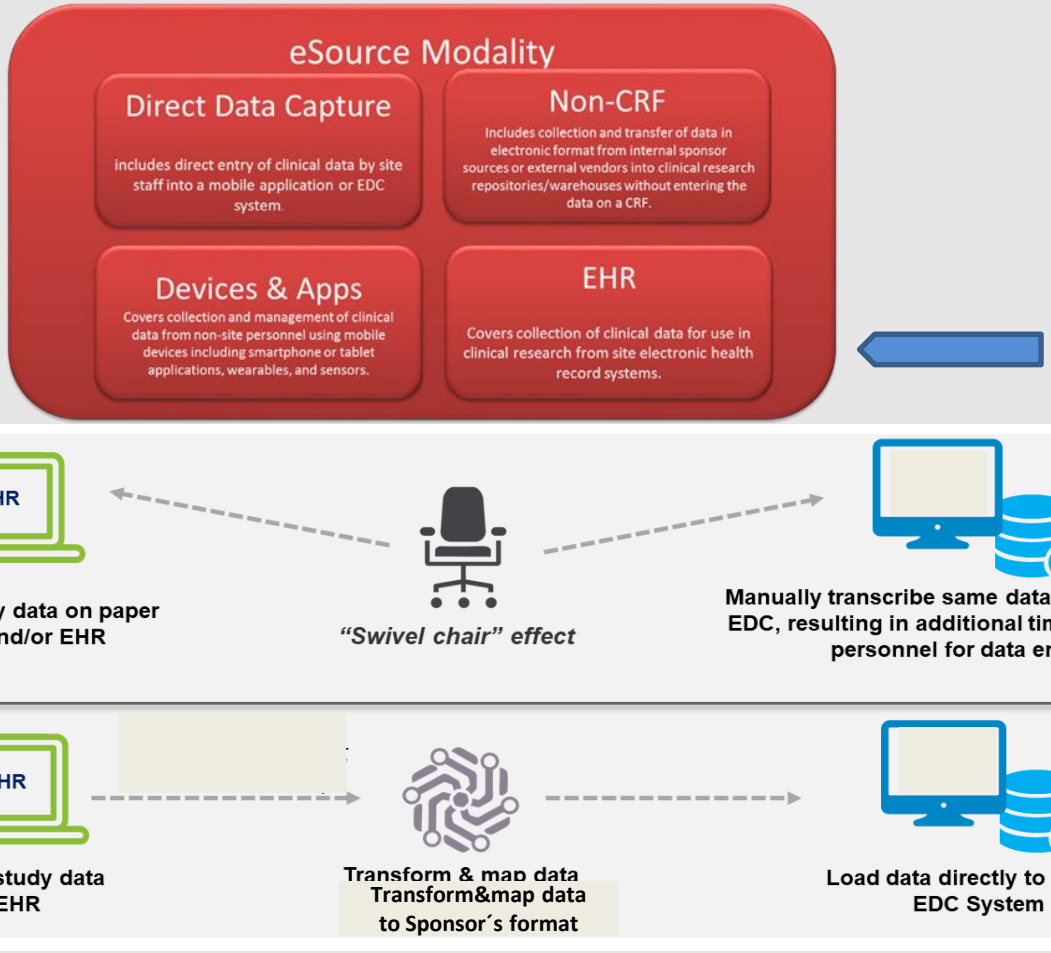
WHAT DE WE NEED FROM SITES?

- ✓ Same SITE/INVESTIGATORS responsibilities.
- ✓ DATA QUALITY - reduced source data verification means increased accountability and quality control by the site of study data.
- ✓ TIMELY DATA ENTRY - is essential to support the early signal detection → <5 days → adequate Study Coordinator resources.
- ✓ FLEXIBLE MONITORING (on site + remote) & trust on new Risk based study execution principles.

BENEFITS

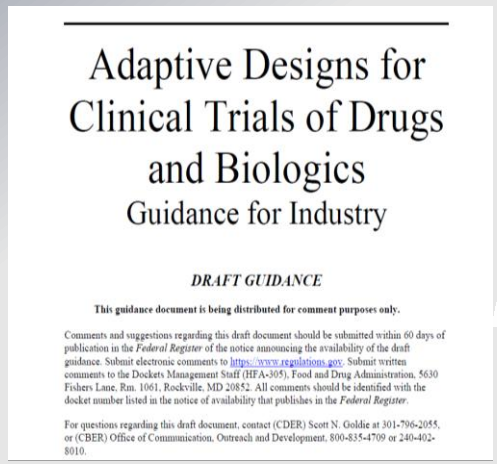
- ✓ Early safety signal detection
- ✓ Timely review of data (More efficient analysis of data across subjects)
- ✓ Early identification of errors (Prevent reocurrence. Reduced queries & less workload during data analyses/locks)

Historias clínicas electrónicas



- Reducir o eliminar la entrada de datos
- Mejorar en la calidad de los datos
- Acceso más rapido a los datos
- Disminuir la carga para los centros y los equipos.

Regulación abierta a diseños innovadores



Adaptive Designs for Clinical Trials of Drugs and Biologics

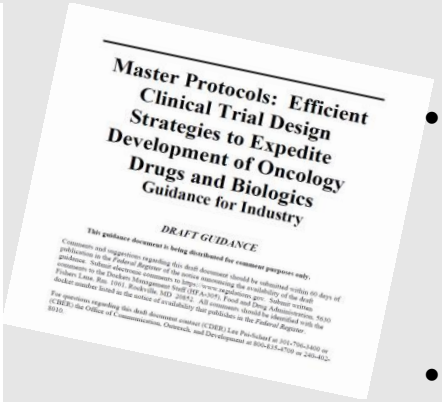
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

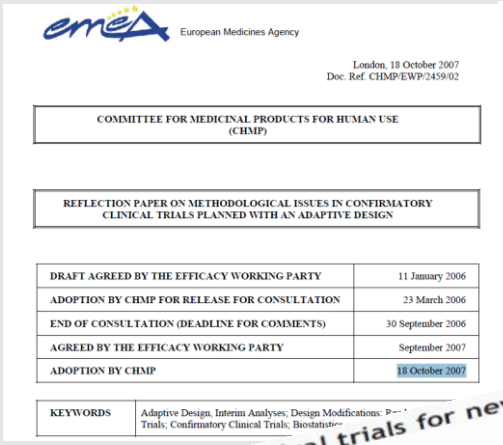
For questions regarding this draft document, contact (CDER) Scott N. Goldie at 301-796-2055, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.



Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE



European Medicines Agency

London, 18 October 2007
Doc. Ref. CHMP/EWP/2459/02

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

REFLECTION PAPER ON METHODOLOGICAL ISSUES IN CONFIRMATORY CLINICAL TRIALS PLANNED WITH AN ADAPTIVE DESIGN

DRAFT AGREED BY THE EFFICACY WORKING PARTY	11 January 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	23 March 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 September 2006
AGREED BY THE EFFICACY WORKING PARTY	September 2007
ADOPTION BY CHMP	18 October 2007

KEYWORDS	Adaptive Design, Interim Analyses, Design Modifications: R... Trials, Confirmatory Clinical Trials, Biostatist...

Clinical Trials Facilitation and Coordination Group CTFG

Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials

12 February 2019

Adaptive clinical trials for new drug applications in Japan☆

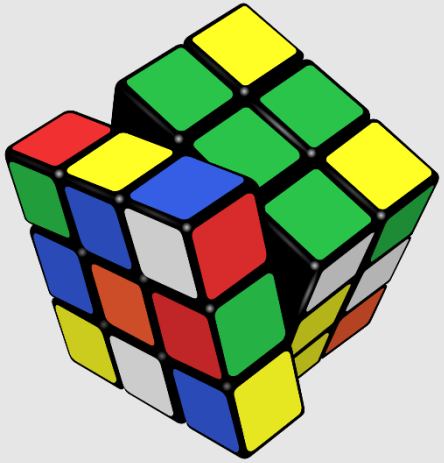
Yuki Ando[a,*], Akihiro Hirakawa[b], Yoshiaki Uyama[c]

[a] Office of New Drug II, Pharmaceuticals and Medical Devices Agency, Japan
[b] Office of New Drug V, Pharmaceuticals and Medical Devices Agency, Japan
[c] Office of New Drug III, Pharmaceuticals and Medical Devices Agency, Japan

Received 5 July 2010; accepted 9 September 2010

- Draft guidance **by FDA** "Adaptive design clinical trials for drug and biologics draft guidance" (September 2018)
- Reflection paper **by EMA** "Reflection paper on methodological issues in confirmatory clinical trials with flexible design and analysis plan" (adoption by CHMP - 18 October 2007)
- Recommendation paper on the initiation and conduct of complex CT by **Clinical Trial Facilitation Group** is a collaboration of European national regulatory agencies
- **Japan PMDA**

Diseño tradicional vs diseño adaptativo



Non-adaptive design - A clinical trial design without any prospectively planned opportunities for modifications to the design.

- Fix the sample size, doses, etc in advance and perform a single efficacy/safety analysis at the end of the study

Adaptive design - A clinical study design that uses accumulated data to decide on how to modify aspects of the study as it continues based on pre-determined decision criteria, without undermining the validity and integrity of the trial

Tipos de diseños adaptativos

More traditional

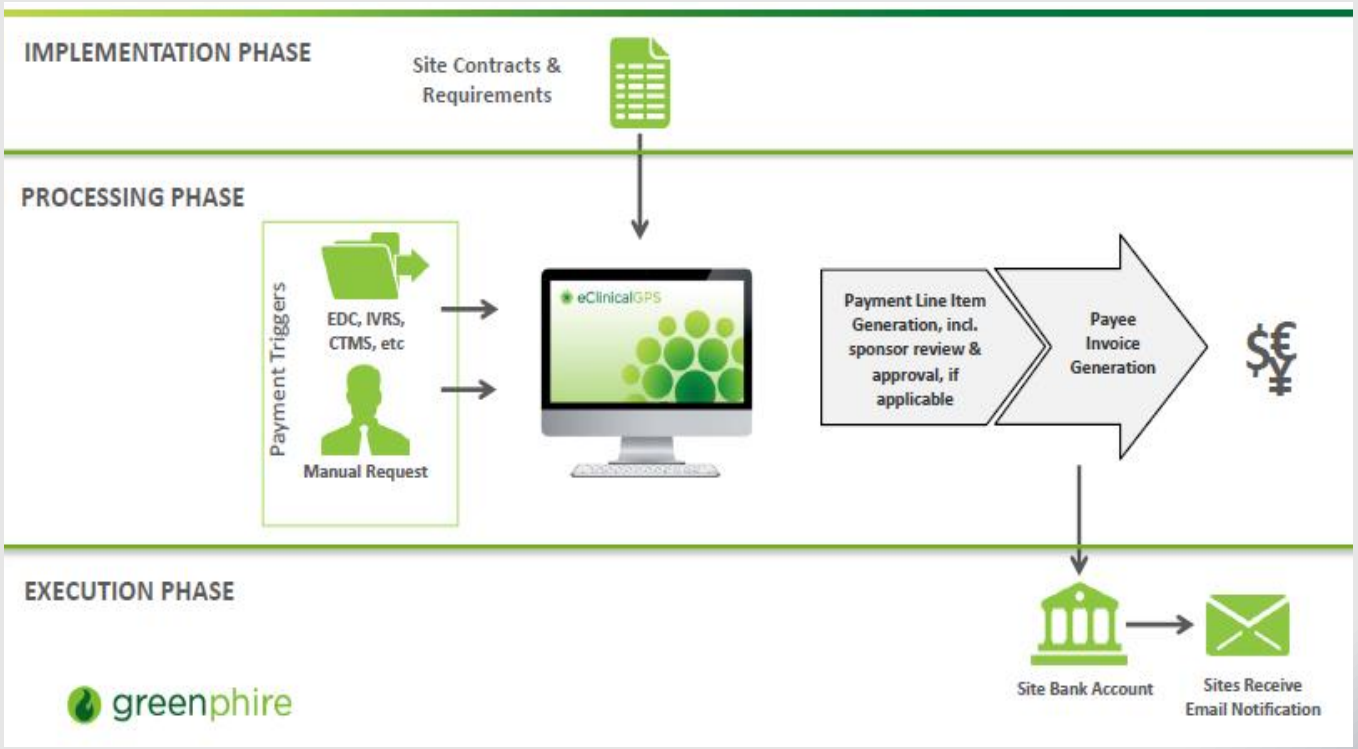
- Study eligibility criteria based on baseline data
- Stopping early for efficacy or futility with group sequential methods
- Blinded sample size re-estimation
- Adaptations based on interim results of an outcome unrelated to efficacy
- Adaptations in the data analysis plan not dependent on within study, between-group outcome differences

Newer

- Dose dropping & stopping for futility
- Adaptive randomization
- Sample size based on interim-effect size estimates
- Population finding
- Endpoint selection
- Seamless phases
- Platform trials
  - Investigate multiple drugs in the same indication or disease condition
- Basket trials
  - Investigate one drug in multiple indications / subtypes of disease conditions

Plataformas tecnológicas: Greenphire

- **Greenphire-eClinical Global Payment System:** sistema web para realizar pagos en respuesta a datos enviados por el centro a través de los CRDe.



Plataformas tecnológicas: InSite y TriNetX

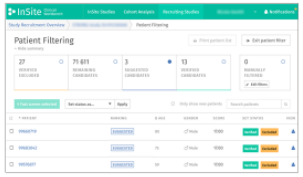
Plataformas en red que utilizan **real-world data** para hacer frente a los retos de la investigación clinica actual y **conseguir tratamientos innovadores de forma más rápida y eficiente**.

InSite throughout the CT life-cycle

A platform for trustworthy re-use of EHR data to support innovation in clinical research.

Study Design | Study Feasibility | Study Placement | Patient Recruitment | EHR to eCRF

- Services for sponsors through InSite online platform
- Based on distributed querying and analytics technology



- Computer supported recruitment for PIs at sites
- Site performance tracking for sponsors

Plataformas tecnológicas: Insite y TriNetX

Optimize Clinical Research

Analyze Real-World Data

TriNetX Live™

Apply a Data-Driven Approach for Clinical Trial Optimization

- Real-time scenario modeling for protocol feasibility
- Directly connect with sites on trial opportunities
- Self-service access to fresh patient data

HCO	Patients in Cohort
Anonymous Site	169,460
Anonymous Site	110,480
Anonymous Site	103,870
Anonym	

HCO	Historic	Predicted
Anonymous Site	3,344	3,053

Trend

TriNetX Research™

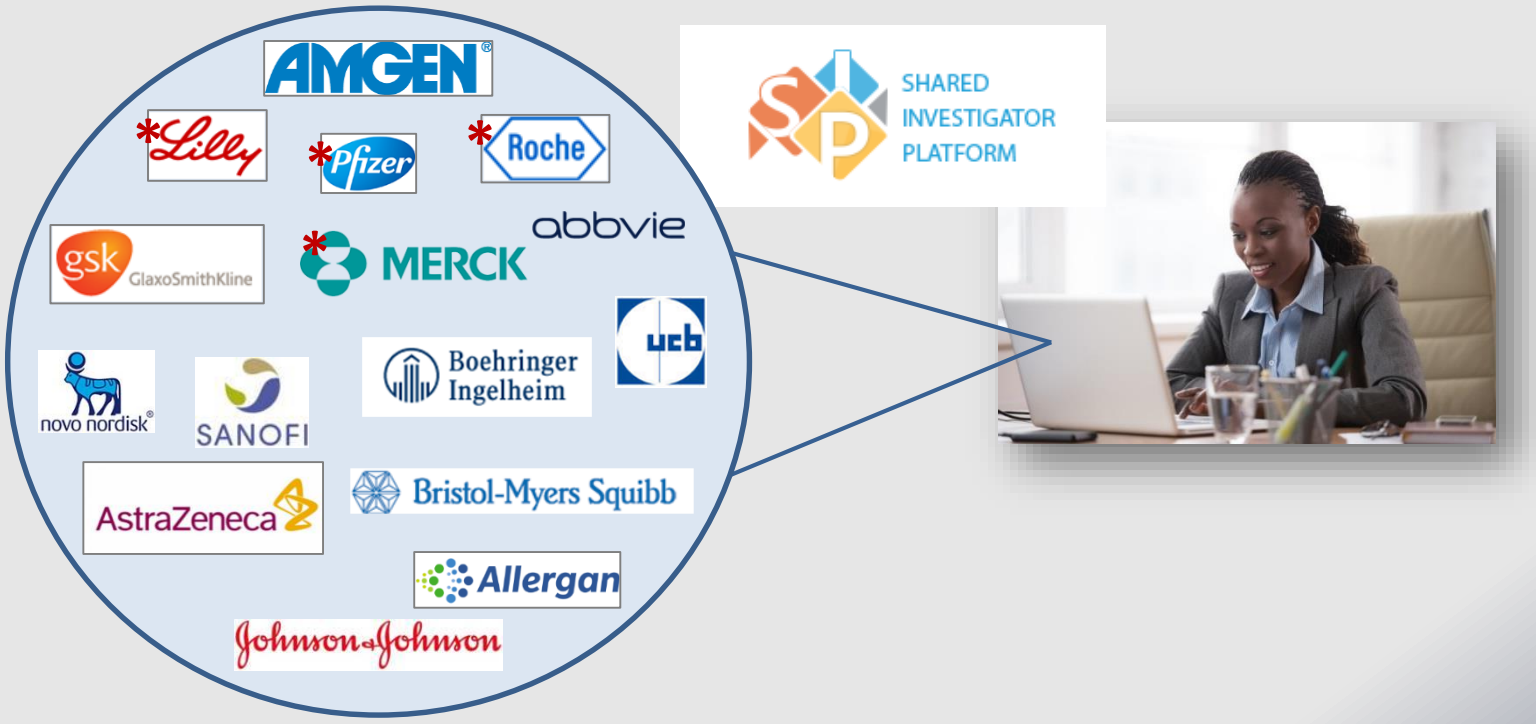
Hypothesize and Answer Complex Research Questions About Patient Outcomes & Treatment Effectiveness

- Access longitudinal clinical and genomic data
- Explore and compare cohorts, review cohort characteristics and compare outcomes of interest
- License and download billions of up-to-date, de-identified clinical facts for analysis with your own analytic tools

Attract Sponsored Trials & Collaborate

Plataformas tecnológicas: SIP

SIP Shared Investigator platform (TransCelerate). SIP is a platform that highlights solutions to make the life of a site investigator easier when conducting clinical studies.



*Adopted SIP

Plataformas tecnológicas: SIP

Unmet Need

- Clinical trial sites use many different websites with unique login credentials to communicate with their Sponsors
- Site staff prepare and provide the same information to each of their Sponsors
- This is time consuming, cumbersome, and often difficult

Objective

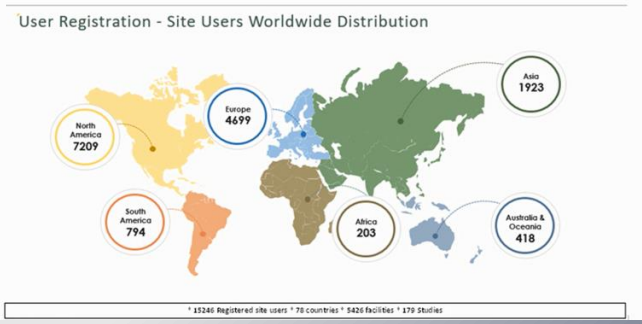
- Reduce the burden on investigative sites
- Provide a central point of access, harmonized content and services, and streamlined interaction with participating clinical trial Sponsors

Benefits

- Revolutionize site-sponsor relationships by enabling a single experience
- Easy-to-use portal
- Allow investigators to spend more time on patients

- ✓ Single Sign on
- ✓ User / Facility profile
- ✓ Study Workspace (Sponsor specific)
- ✓ Feasibility survey
- ✓ Training
- ✓ Document management
- ✓ Study Activation
- ✓ Investigator payments
- ✓ Task, alerts, notification
- ✓ Safety notification
- ✓ Dashboards / News /Metrics

User Registration (as of 11 Feb. 2019)



Digitalización: herramientas para el paciente

Representative Points of Mobile / Digital Interaction

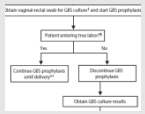
Recruitment

Challenge: *Difficulty finding sufficient subjects to screen and enroll*

Tools:
Digital tools Supporting Recruitment & Referrals

Value: *Improved access to patients and accelerated study start-up*

Screening



Challenge: *Complex I/E Screening Criteria*

Tools:
Investigator-Facing I/E Screening Tool

Value: *More efficient / streamlined screening*

Consent

Challenge: *Low literacy levels and difficulty managing informed consent (IC) versioning*

Tools:
eConsent / re-Consent

Value: *Improved quality of IC and levels of patient literacy with consent language; Improved IC audit performance*

Retention & Compliance

Challenge:
Missed medications and visits; low compliance with protocol

Tools:
Compliance Toolkit
(medication reminders, appt tracking & reminders, visit & dosing information, content library)

Value: *Improved compliance & retention*

Continuous Engagement & Tracking

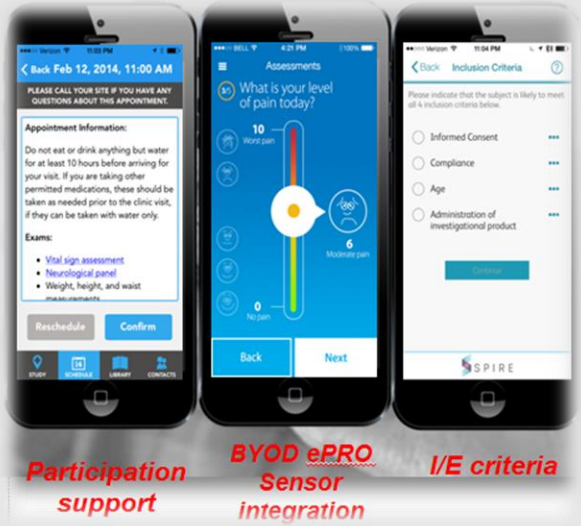
Challenge: *Limited view of patient condition between clinic visits*

Tools:
- ***ePRO*** *(supporting BYOD)*
- ***Sensor Data Capture***
- *Patient-Site Communication Tools*
- *Integration with PfizerLink*
- *Safety Monitoring*

Value: *Capture of new endpoints, Improved understanding of patient condition/experience between visits*

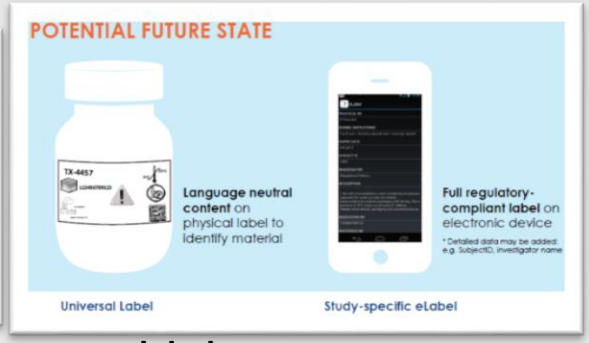
Digitalización: herramientas para el paciente

Wearable devices



Apps, BYOD (bring your own devices)

eConsent



elabels

FDA News Release

FDA approves pill with sensor that digitally tracks if patients have ingested their medication

New tool for patients taking Abilify

For Immediate Release

November 13, 2017

Summary

FDA approves Abilify MyCite, a pill with a sensor that digitally tracks if patients have ingested their medication

Release

The U.S. Food and Drug Administration today approved the first drug in the U.S. with a digital ingestion tracking system. Abilify MyCite (aripiprazole tablets with sensor) has an ingestible sensor embedded in the pill that records that the medication was taken. The product is approved for the treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder and for use as an add-on treatment for depression in adults.

The system works by sending a message from the pill's sensor to a wearable patch. The patch transmits the information to a mobile application so that patients can track the ingestion of the medication on their smart phone. Patients can also permit their caregivers and physician to access the information through a web-based portal.

"Being able to track ingestion of medications prescribed for mental illness may be useful for some patients," said Mitchell Mathis, M.D., director of the Division of Psychiatry Products in the FDA's Center for Drug Evaluation and Research. "The FDA supports the development and use of new technology in prescription drugs and is committed to working with companies to understand how technology might benefit patients and prescribers."

It is important to note that Abilify MyCite's prescribing information (labeling) notes that the ability of the product to improve patient compliance with their treatment regimen has not been shown. Abilify MyCite should not be used to track drug ingestion in "real-time" or during an emergency because detection may be delayed or may not occur.

5. Conclusiones

Conclusiones

- **Entorno competitivo y cambiante** → país preferente.
- **Identificar centros de excelencia en investigación** → imprescindible para seguir atrayendo investigación a España.
- **Equipos multidisciplinares profesionalizados , calidad de los datos y pacientes reclutados**→ clave del éxito
- **Acortar tiempo de desarrollo de los fármacos** → en beneficio para los pacientes, es nuestro objetivo.
- **La Innovación es una realidad** → hay que estar preparados para ello, sin digitalización no hay futuro.


¡Gracias!

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