Update on implementation of the Clinical Trial Regulation

How will the New Common Law on Clinical Trials in EU Facilitate Paediatric Research?

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European network of paediatric research at the EMA (Enpr-EMA)
London, June 7 2018

Conventions and guidelines to take into consideration in paediatric research…

Convention on Rights of Child

UN

Convention for Protection of Human Rights and Dignity CE, Oviedo

Four general principles :

- beneficence
- non-maleficence
- respect for individual
- justice

Declaration of Helsinki WMA

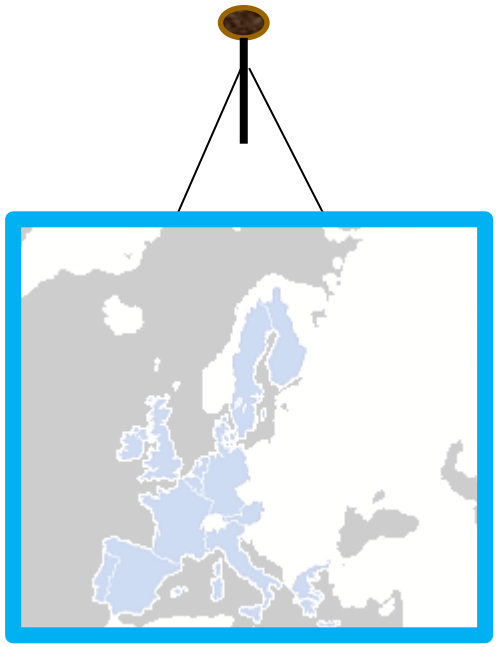
Guideline Clinical Investigation in Paediatrics ICH E11

Ethical guidelines – research in humans CIOMS, WHO

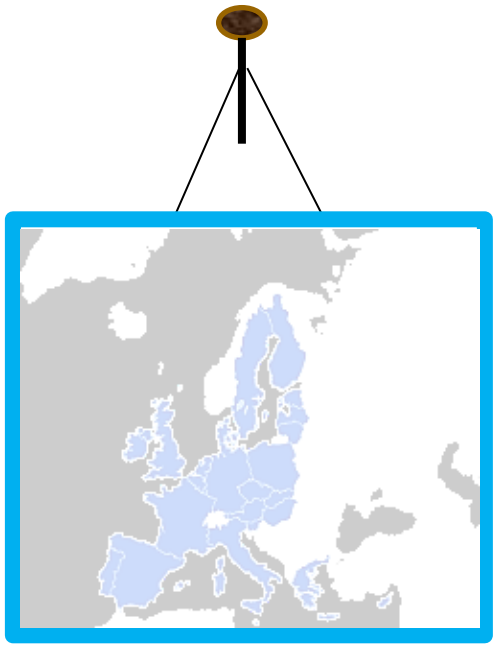
Good Clinical Practice ICH E6 (R3)

More rules….

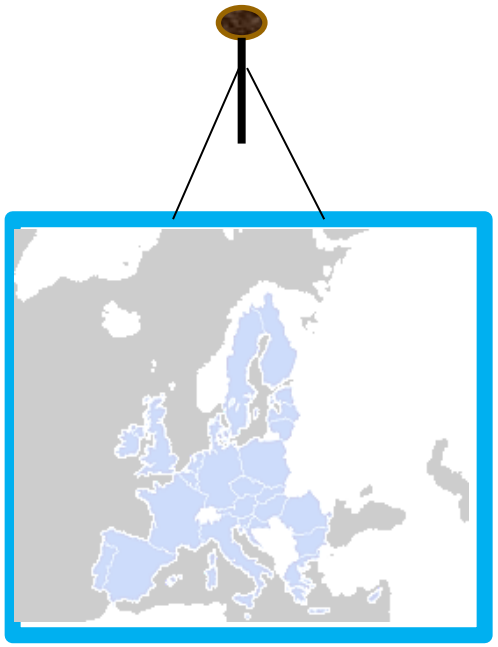
Legal situation - Clinical Trials on Medicinal Products in EU



Before 2004…



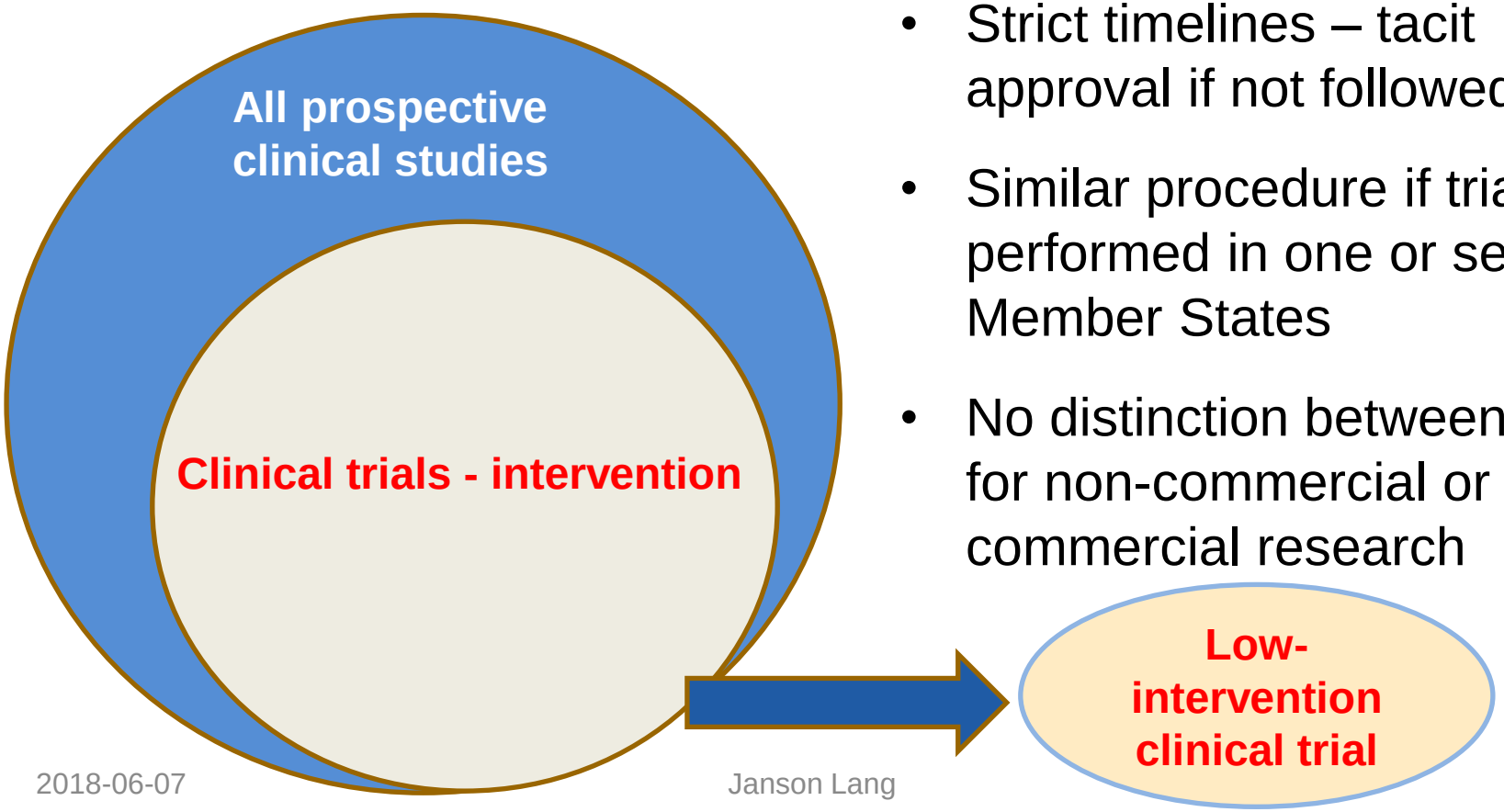
Directive 2001/20/EC



Regulation (EU) No 536/2014

Clinical studies on efficacy and safety of medicinal products

Clinical Trials Regulation key points



- Also in future national decisions - one per Member State
- Strict timelines – tacit approval if not followed
- Similar procedure if trial performed in one or several Member States
- No distinction between rules for non-commercial or commercial research

EU Portal – database 1(2)

- All applications in future – submission through common EU Portal set up and managed by the European Medicines Agency (EMA)
- No future separate application to ethics committees or national competent authorities
- Database archive of all records uploaded to EU Portal
- New legislation will apply when EMA Portal and database are fully functional (in two ys?)

EU Portal – database 2(2)

All entries publicly accessible except

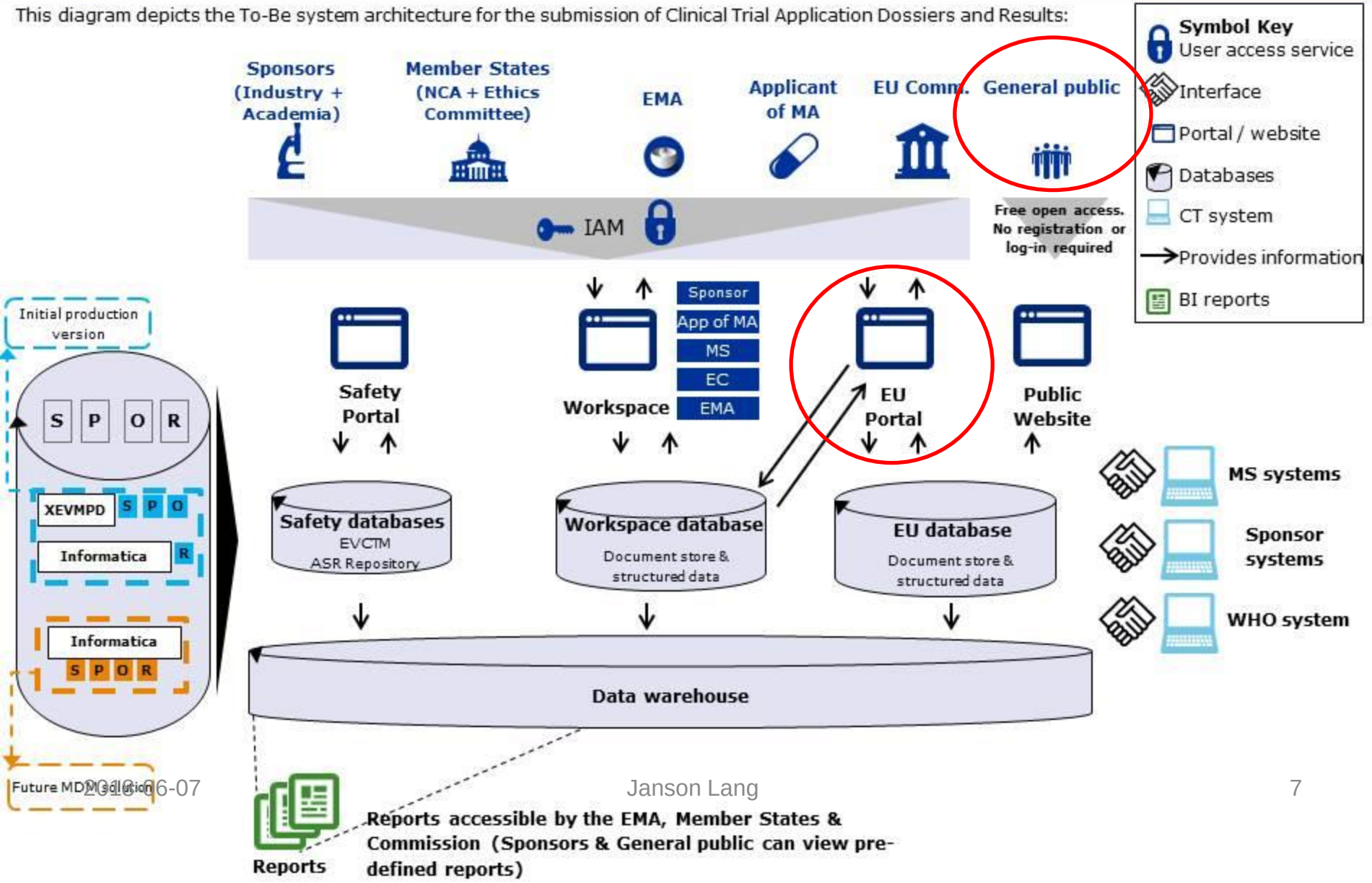
- personal data
- commercially confidential information unless overriding public interest in disclosure
- draft versions of the assessment reports
- information necessary for supervision of trial

Sponsor's documents and assessment reports by Member States are public - delay of publication depends on development phase of medicinal product

Business context view

EUROPEAN MEDICINES AGENCY

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



Clinical Trials Regulation (EU) No 536/2014
Eight steps facilitating paediatric clinical trials 1(2)

Applications – new clinical trial or substantial modification of trial

Conduct of trial

Publication of trial results

Clinical Trials Regulation (EU) No 536/2014
Eight steps facilitating paediatric clinical trials 1(2)

Application – new clinical trial or substantial modification of trial

Conduct of trial

Publication of trial results

1. Simplified procedure - single application and one decision per Member State via EU Portal and Database
2. Multinational trials - collaboration between Member States assessing risks and benefits (protocol, IB) and pharmaceutical quality issues including GMP
3. Shorter and defined timelines for assessment and decision
4. Multiple Co-sponsors possible
5. Informed consent – same legal basis in EU/EEA – possibility to defer informed consent in emergency situations

Clinical Trials Regulation (EU) No 536/2014
Eight steps supporting paediatric clinical trials 2(2)

Application – new clinical trial or substantial modification of trial

Conduct of trial

Publication of results

6. Simplified procedures for low-intervention clinical trials
7. Trial safety collaboration between Member States, simplified safety reporting for low-intervention trials, web-based SUSAR reporting tool

Clinical Trials Regulation (EU) No 536/2014
Eight steps supporting paediatric clinical trials 2(2)

Application – new clinical trial or substantial modification of trial

Conduct of trial

Publication of trial results

8. Transparency of results including application dossiers and assessment reports

Applications – new clinical trial or substantial modification of trial

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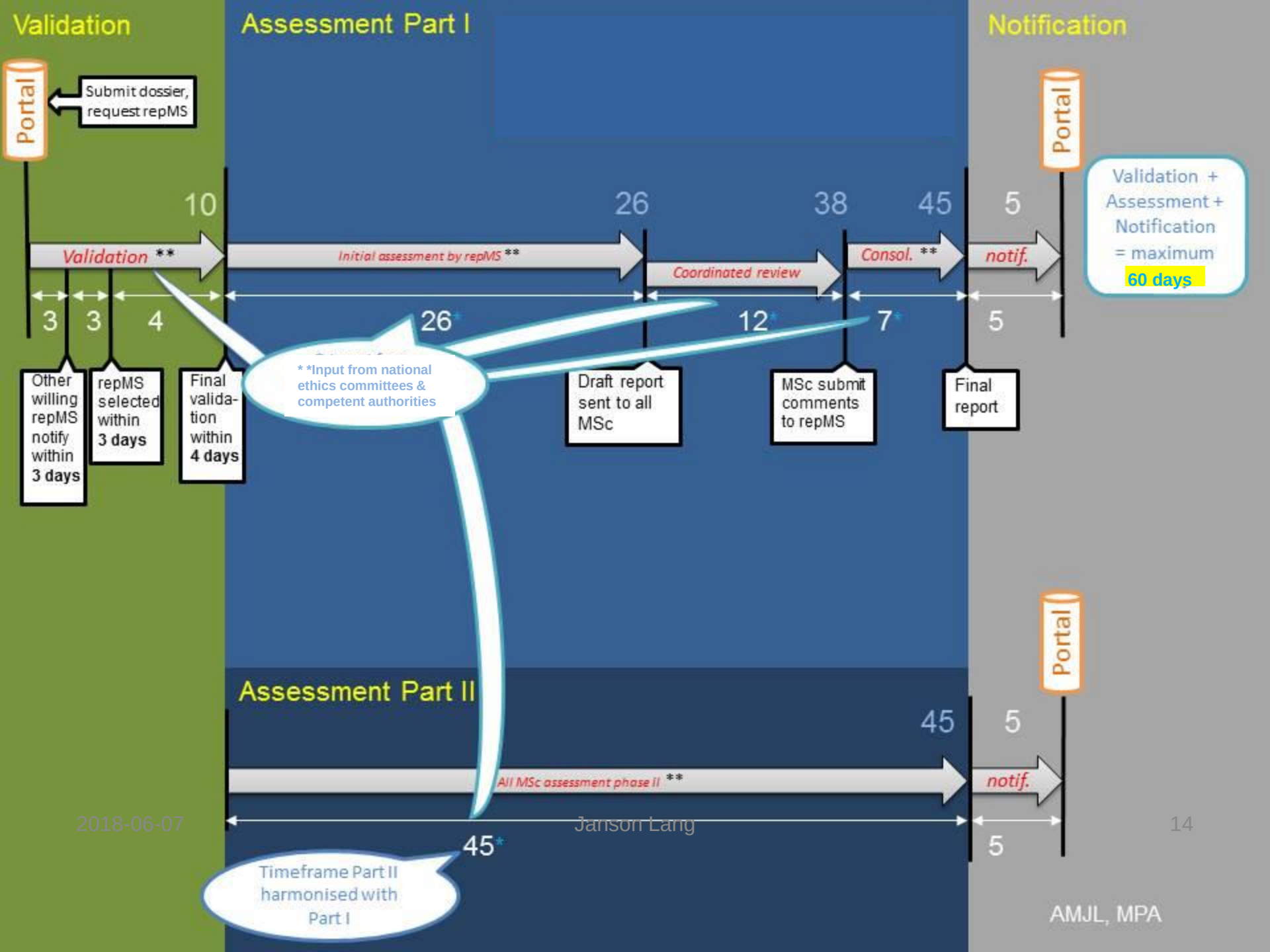
Part I and Part II of Application Dossier sent to EU Portal administered by EMA

Part I Protocol, Investigator's Brochure, details on GMP etc.

Multinational trials one Reporting Member State for Part I

Part II National issues – insurance, compensation, investigator CV etc.


Validation
Assessment Part I
Notification
Portal
Submit dossier, request repMS
10
26
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Validation **
Initial assessment by repMS **
Coordinated review
Consol. **
notif.
Portal
Validation + Assessment + Notification = maximum 60 days
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Other willing repMS notify within 3 days
repMS selected within 3 days
Final validation within 4 days
* *Input from national ethics committees & competent authorities
Draft report sent to all MSc
MSc submit comments to repMS
Final report
Assessment Part II
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All MSc assessment phase II **
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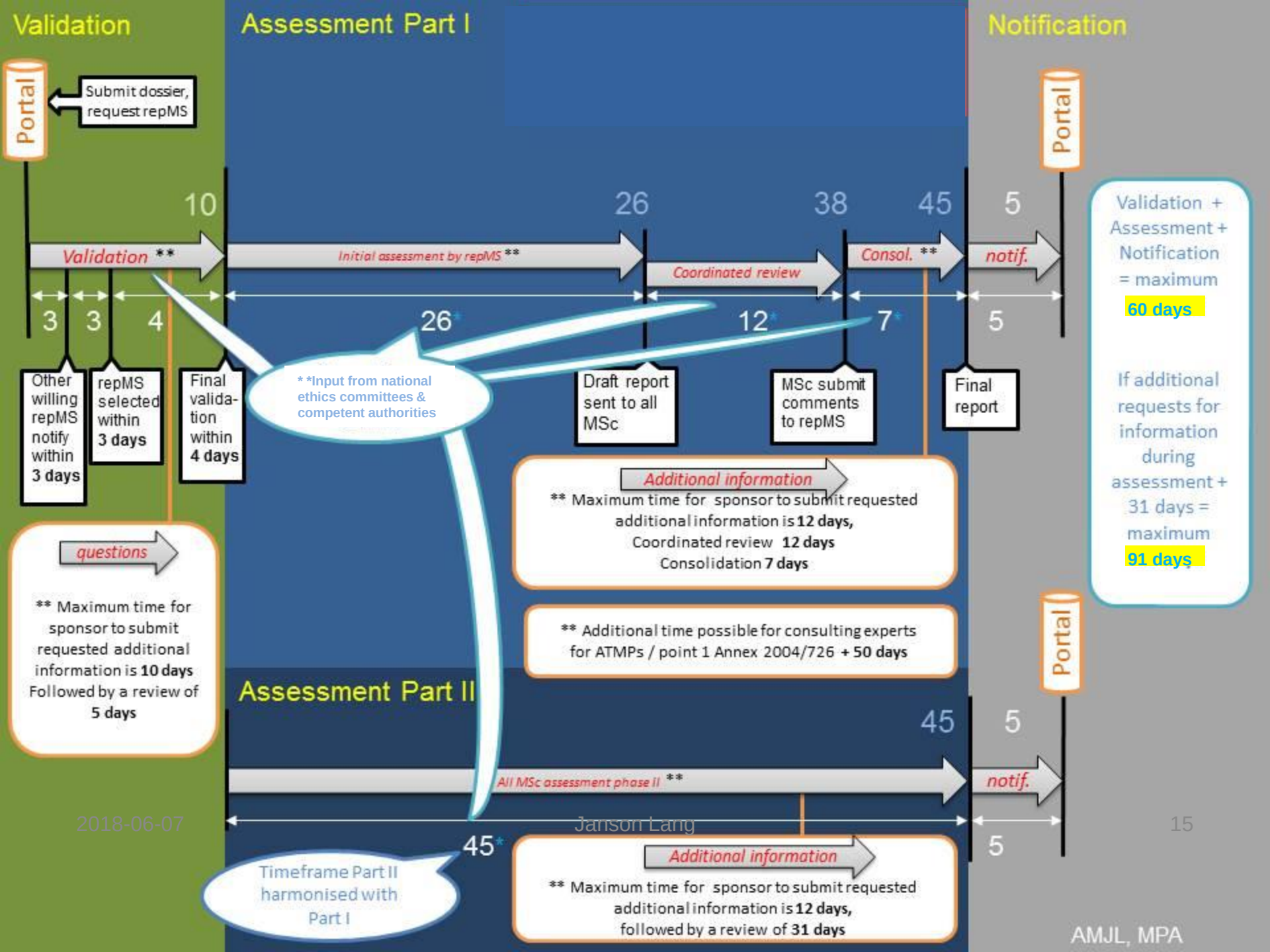
Timeframe Part II harmonised with Part I
AMJL, MPA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notif.
Portal
Validation + Assessment + Notification = maximum 60 days
If additional requests for information during assessment + 31 days = maximum 91 days
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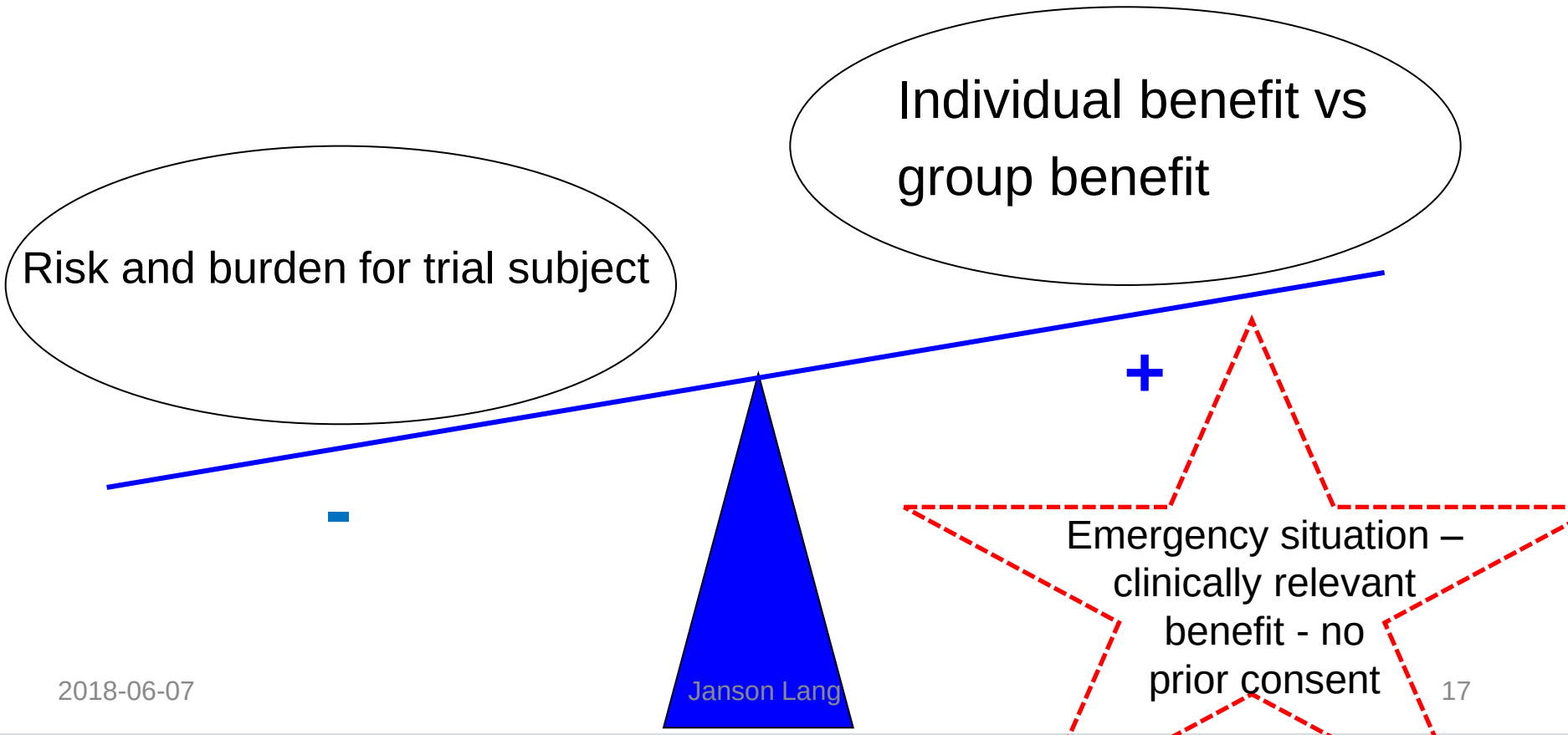
Other willing repMS notify within 3 days
repMS selected within 3 days
Final validation within 4 days
* *Input from national ethics committees & competent authorities
Draft report sent to all MSc
MSc submit comments to repMS
Final report
Additional information
** Maximum time for sponsor to submit requested additional information is 12 days,
Coordinated review 12 days
Consolidation 7 days
questions
** Maximum time for sponsor to submit requested additional information is 10 days
Followed by a review of 5 days
** Additional time possible for consulting experts for ATMPs / point 1 Annex 2004/726 + 50 days
Assessment Part II
45
5
All MSc assessment phase II **
notif.
Portal
45*
5
Timeframe Part II harmonised with Part I
Additional information
** Maximum time for sponsor to submit requested additional information is 12 days,
followed by a review of 31 days
AMJL, MPA

Applications – new clinical trial or substantial modification of trial

5. Informed consent – same legal basis in EU/EEA – possibility to defer informed consent in emergency situations

Part I and Part II of Application Dossier sent to EU Portal administered by EMA but all decisions continue to be national



Chapter V of Clinical Trial Regulation
Protection of subjects and informed consent

- Details on informed consent procedure and prior interview
- Special rules on pregnant or breastfeeding women
- Special rules for minors and subjects in emergency situations

Minors – legal basis on information and consent

- Informed consent by legal representative (-s)
- Minors must obtain information adapted to their age and mental maturity by investigator or personnel trained in communicating with children
- Explicit wish of subject must be respected
- No financial incentives
- No alternative wyas available to obtain results from subjects with decision making capacity
- Direct benefit for subject or some benefit for group of patients with same condition

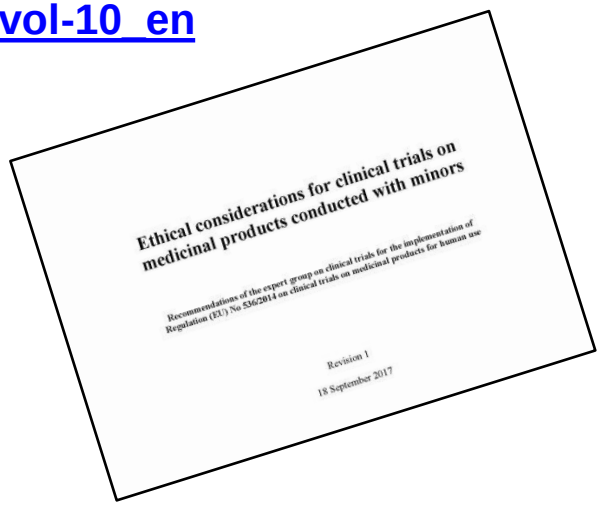
Minors in emergency situations – informed consent after first trial-specific intervention

- Sudden situation, life-threatening or serious medical condition, therapeutic window does not allow prior consent
- Scientific grounds to expect direct clinically relevant benefit
- Trial relates to condition causing the emergency
- Minimal risk compared to normal clinical practise
- Consent sought without delay after intervention

Ethical considerations for clinical trials on medicinal products conducted with minors

https://ec.europa.eu/health/documents/eudralex/vol-10_en

- Chapter V Additional information
- Document published September 2017



- Benefit vs risk and burden
- Paediatric age groups and level of maturity
- Assent vs agreement
- Withdrawal of consent
- Staggered approach – trial performed sequentially in different age groups
- Legally designated representative
- Stopping rules
- Sexual counseling, pregnancy risk

Conduct of trial

6. Simplified procedures for low-intervention clinical trials

e.g. GCP adapted to nature of the trial:

- monitoring
- contents of trial master file
- traceability of investigational medicinal products

Low-intervention clinical trial

- investigational medicinal products with marketing authorisation (except placebo)
- protocol states that the medicinal products use is
  - according to terms of the marketing authorisation or
  - supported by published scientific evidence on safety and efficacy
  - interventions (additional diagnostics or monitoring) with limited additional risk compared to normal clinical practice

Conduct of trial

7. Trial safety collaboration between Member States, simplified safety reporting for low-intervention trials possible, web-based SUSAR reporting tool

Trial safety collaboration between Member States, simplified safety reporting for low-intervention trials, web-based SUSAR reporting tool

- Cooperation between Member States evaluating annual safety reports

- SUSARs possible to report by simplified web-based structured form

Publication of trial results

8. Transparency of results including application dossiers and assessment reports

Publication of trial results

- Avoid unnecessary research replication – prompt publication of results
- Article 41 of the Paediatric Regulation
  - Publication within six months after completion of study
- Article 37 Clinical Trial Regulation
  - summary of results within one year after trial completion
  - full report of trial 30 days after market authorisation decision
  - trial documents including protocol public immediately after decision or deferred in trials of new products in early development

Thanks for your attention – questions welcome!

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