The future clinical trial authorisation process: the new evaluation process

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Agenzia Italiana del Farmaco

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Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

*Massimiliano Sarra, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (25.03.2015) and published on the Official Journal of 15.05.2015 according to EMA policy /626261/2014 on the handling of the conflicts of interest for scientific committee members and experts.

N.B. I am not receiving any compensation

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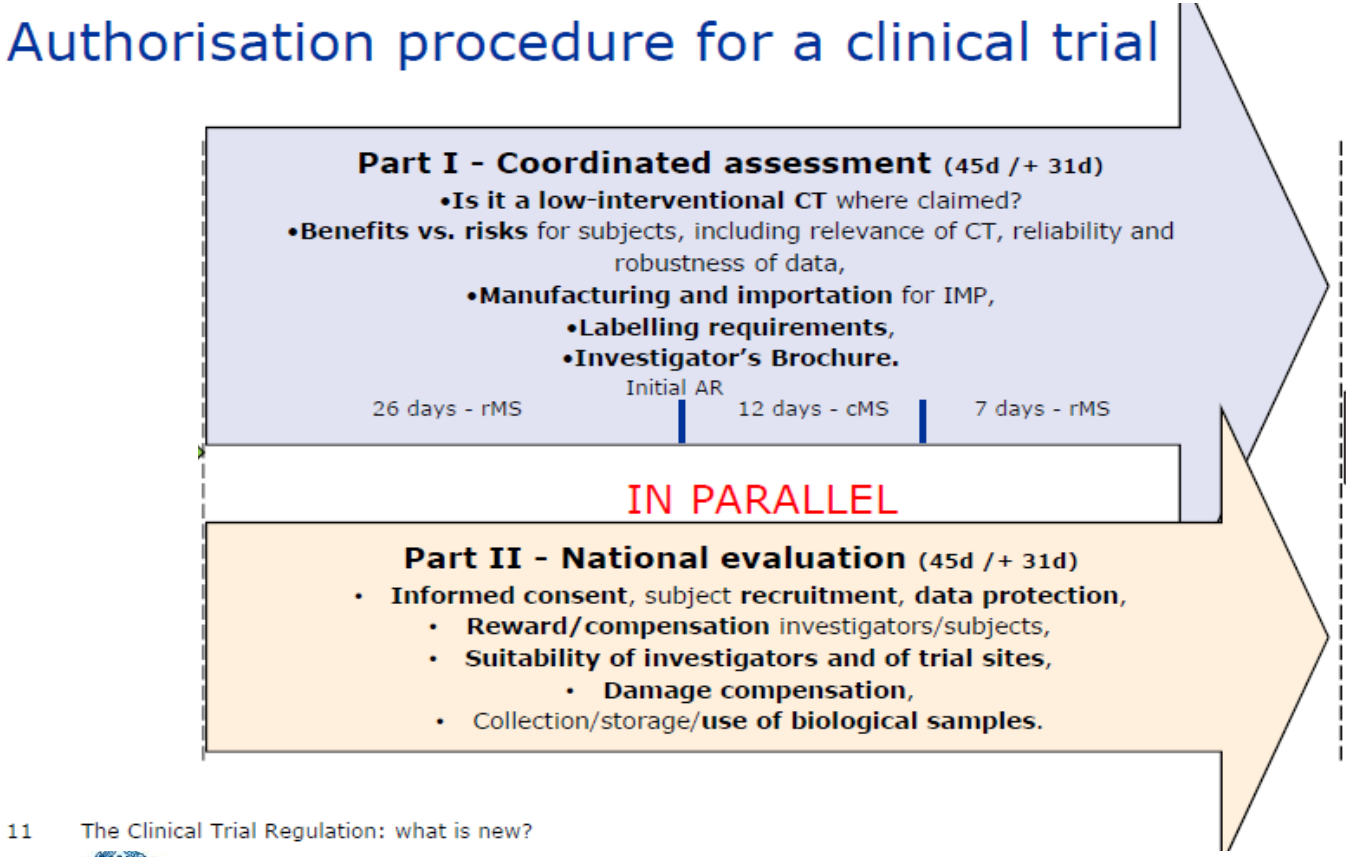
Directive 2001/20/CE

Regulation 536/2014/CE

Schematic overview of the Coordinated Assessment:



11 The Clinical Trial Regulation: what is new?

Assessment 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

Low-intervention clinical trial

(a) the IMPs are authorised;

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

- the IMPs are used in accordance with the marketing authorisa-tion;
- the use of the investigational medicinal products is evidence-based and supported by published scientific evidence

(c) additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden compared to normal clinical practice;

Mononational CT

RMS assesses the aspects of part I, generates an assessment report (AR), and formulates a conclusion (acceptable, acceptable with conditions, not acceptable) between the validation date (D0 and the reporting date (D45).

Multinational CT

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)

Assessment procedure

- D0: validation date of the application
- D26: draft Part I AR made available by the RMS (initial assessment phase)
- D38 (+12): all CMS can share considerations (coordinated review phase)
- D45 (+7): RMS finalizes the Part I AR (consolidation phase); the final assessment report from the RMS submitted to the EU Portal (reporting date)

Request of Additional information by the RMS

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.

ARTICLE 6

Assessment report Part II

- 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

(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

Timeline for Assessment of part II

- 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.

Persons assessing the application

1. Member States shall ensure that assessors:
   - have no conflicts of interest (financial or personal),
   - are independent,
   - are free of any other undue influence.

2. Member States shall ensure that the assessment is done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience.

3. At least one lay-person shall participate in the assessment.

ARTICLE 9

The Voluntary Harmonisation Procedure

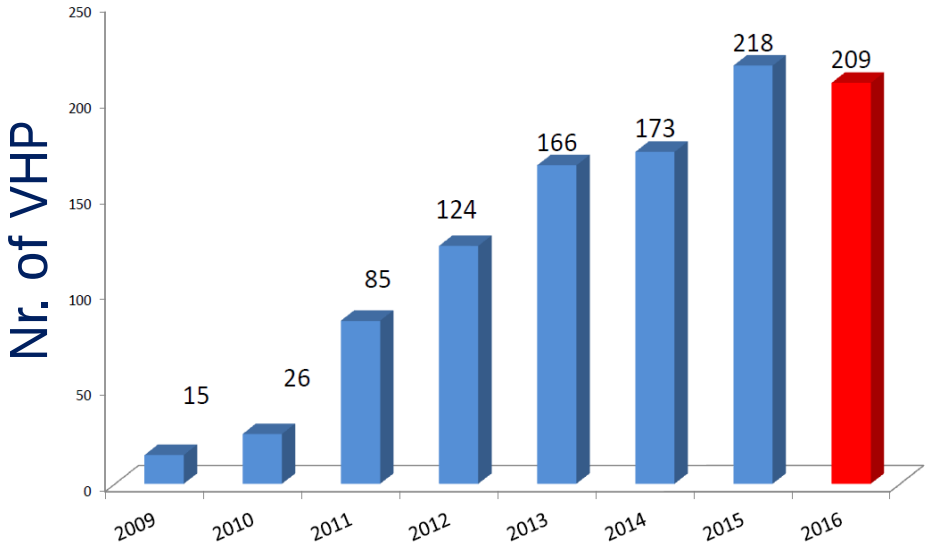
VHP applies to all phase I-IV MN CTs involving 2 or more Member States. It allows the joint assessment of the same documentation provided by the Applicant in a specific timeline, thus leading to the harmonized conclusion on the possibility to approve or reject the CT Application in all the Members States involved.

VHP: Main Characteristcs

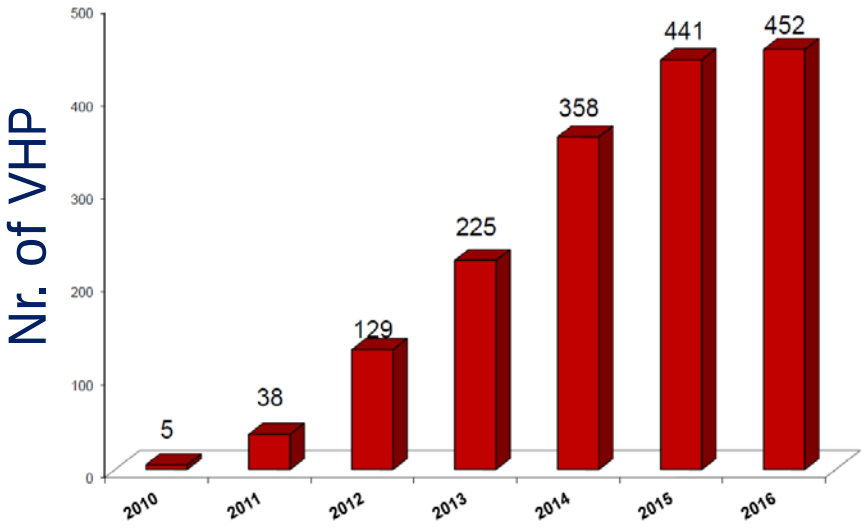
- Harmonization of the Documents (Protocol, IB, IMPD, risk/benefit) shared by the NCA through the VHP-DB
- A rigid and specific Timeline
- Nomination of a Ref-NCA that lead the assessment and collect the comments of the P-NCA
- Single harmonized assessment of the CTA, thus leading to a single harmonized decision among the Member States involved
- A fast-track national authorization

Increasing Numbers of VHP applications

Initial submission



Substantial Amendments



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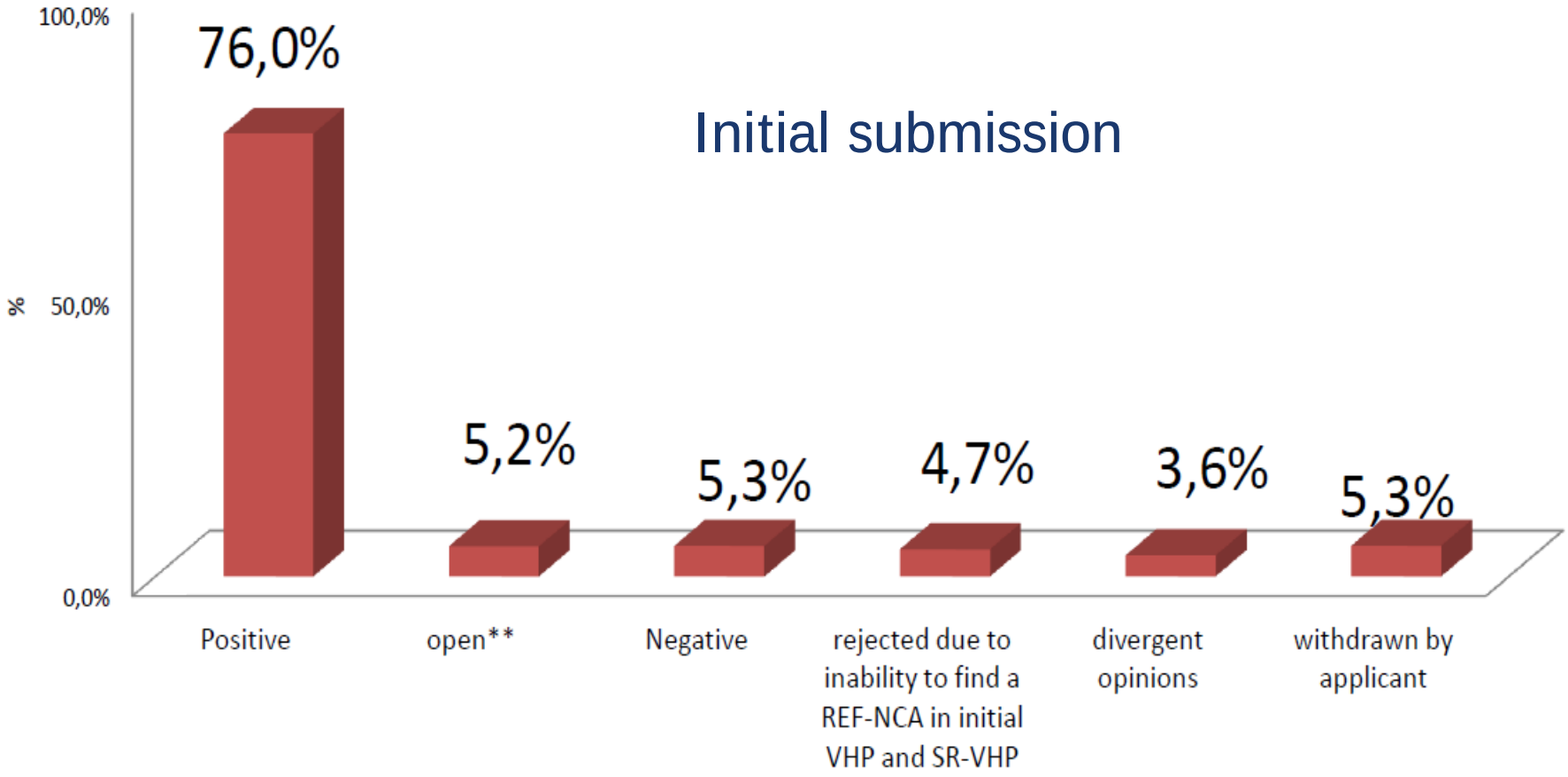
Outcomes of VHP Applications



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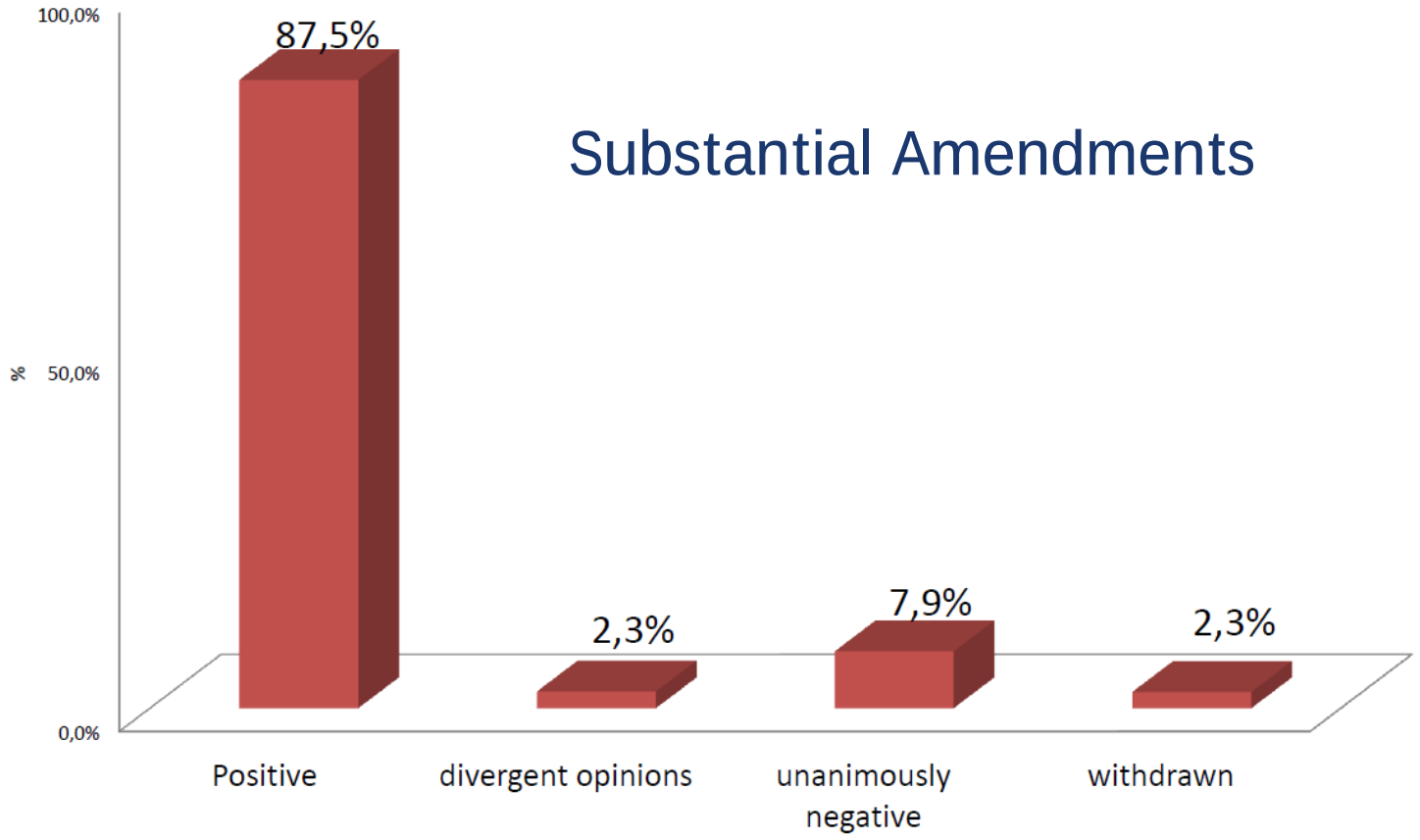
Outcomes of VHP Applications



Substantial Amendments

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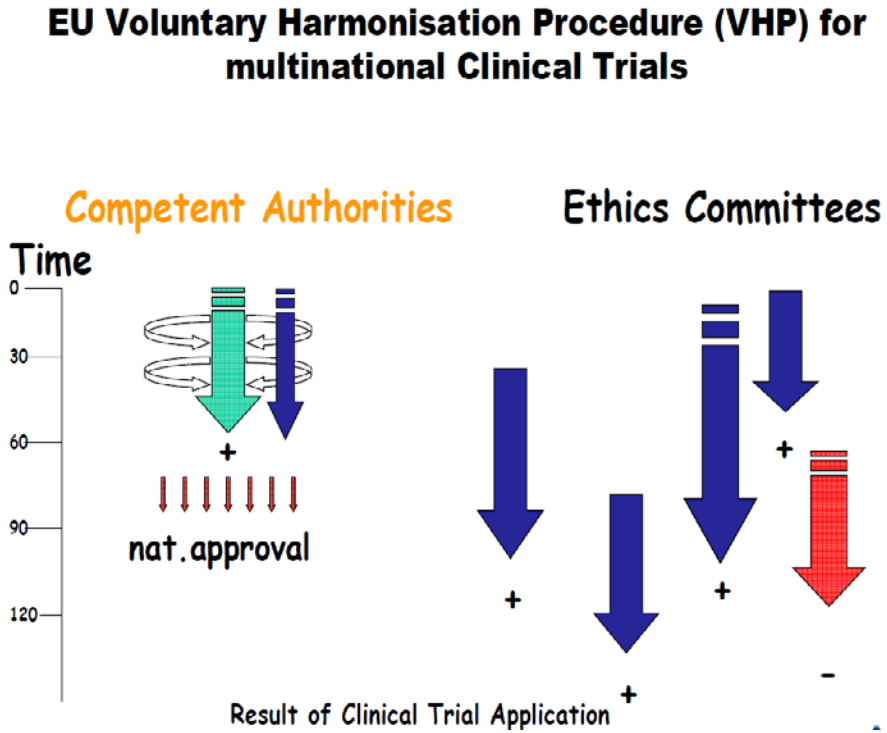
Recent Progresses in VHP Involvment of Ethical committes: VHP Plus



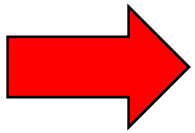
VHP-plus is a VHP involving Ethics Committees in the assessment of benefit/risk, IB and protocol in some Member States

EU Portal and Database

Article 80 and 81 give the European Medicines Agency (EMA) the responsibility to establish an EU Portal and Database.

The Portal and Database will considerably facilitate:

- the application for clinical trials authorization, in particular in case of multinational clinical trials, to the sponsor;
- the assessment carried out by the Member states authorities;
- access to clinical trials information by the general public.

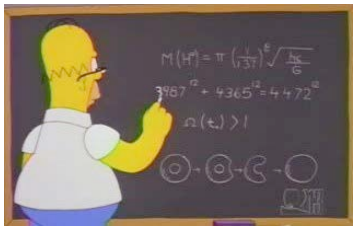


CTFG MS are supporting EMA's portal/IT system development in various working groups.

Assessment Report Templates

- The CTFG has taken on the responsibility to draft new assessment report (AR) templates compliant with the requirements of the new CTR
- The CTFG established a subgroup of Member States collaborating in drafting the new AR templates
- New AR templates have been adopted in June during the CTFG plenary meeting
- The templates are currently under testing in VHP

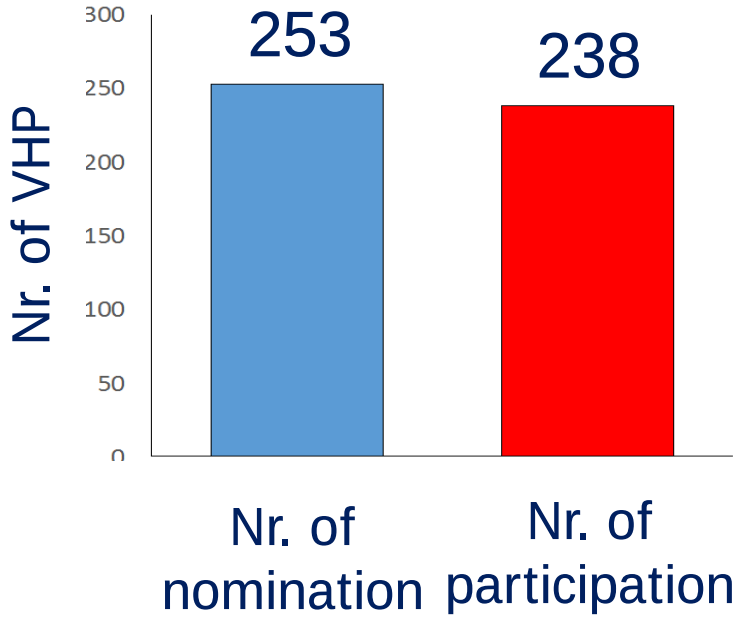
EU Network Training

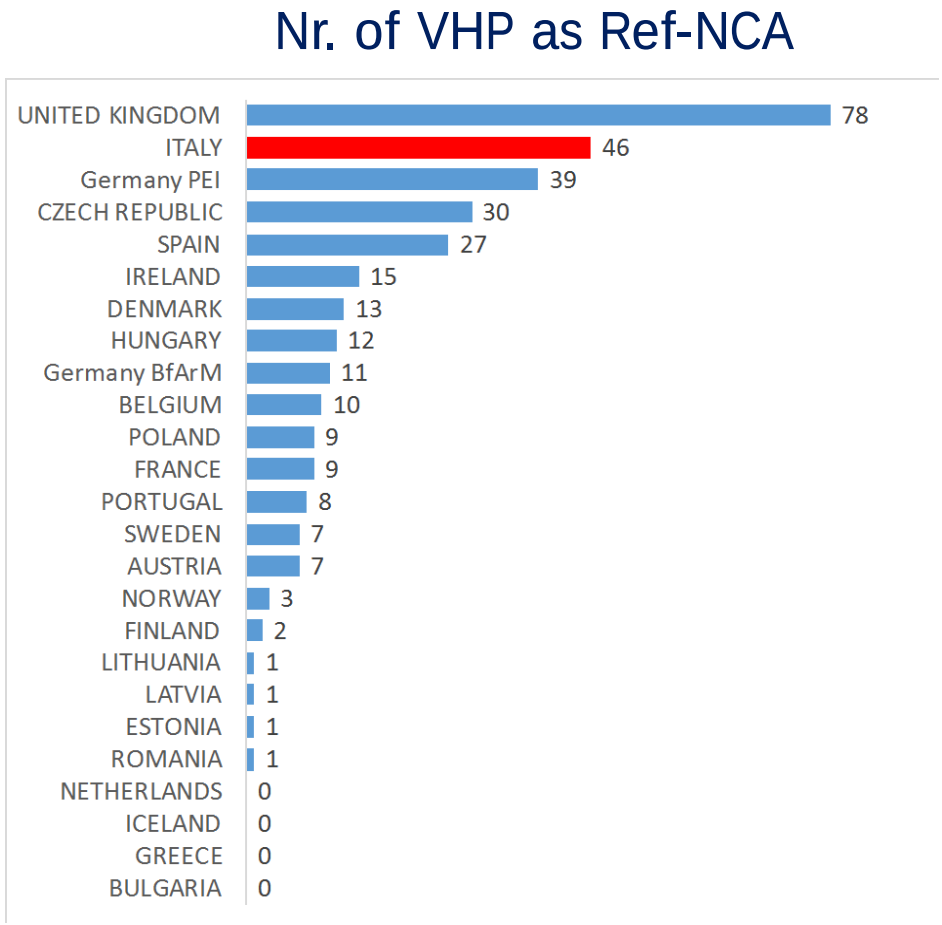


The CTFG in collaboration with EMA (EU Network Training Centre) and single NCA organizes training on topics related to the new regulation

- 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 – 29/30.03.2017)

IT involvement in VHP (2015-2016)





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.

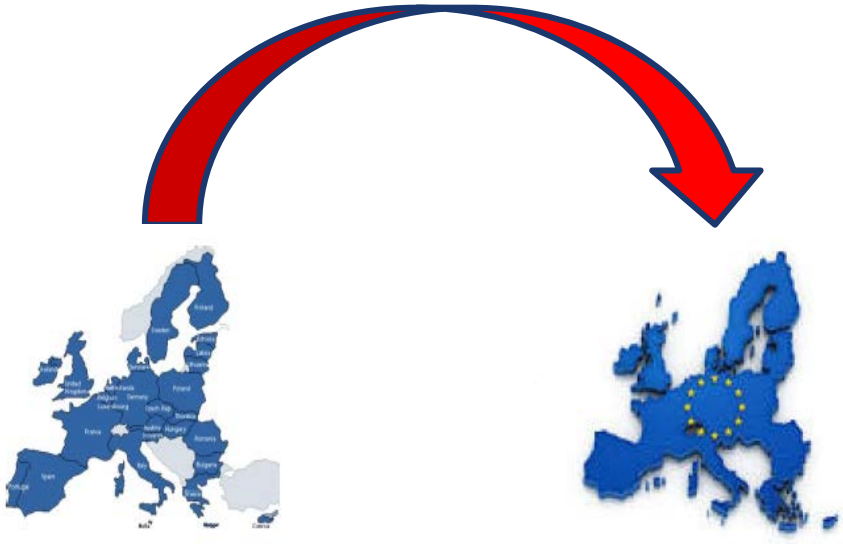
National IT system: OsSC

Summary

- The new procedures for the assessment of MN clinical trials should lead to harmonized documentation.
- Authorization of CT will follow a specific timeline identical for all the MS involved in the procedure.
- The assessment process is consistent with the principle of worksharing already existing for other procedures involving more than one MS
- Documents are submitted and shared through a single web-based EU portal
- The legal form of a Regulation would present advantages for sponsors and investigators, since divergences of approach among different Member States will be kept to a minimum.

Conclusions

New Evaluation Process



2001/20/CE

536/2014/CE

Worksharing

Harmonization

Timeline

Decisions

Documents

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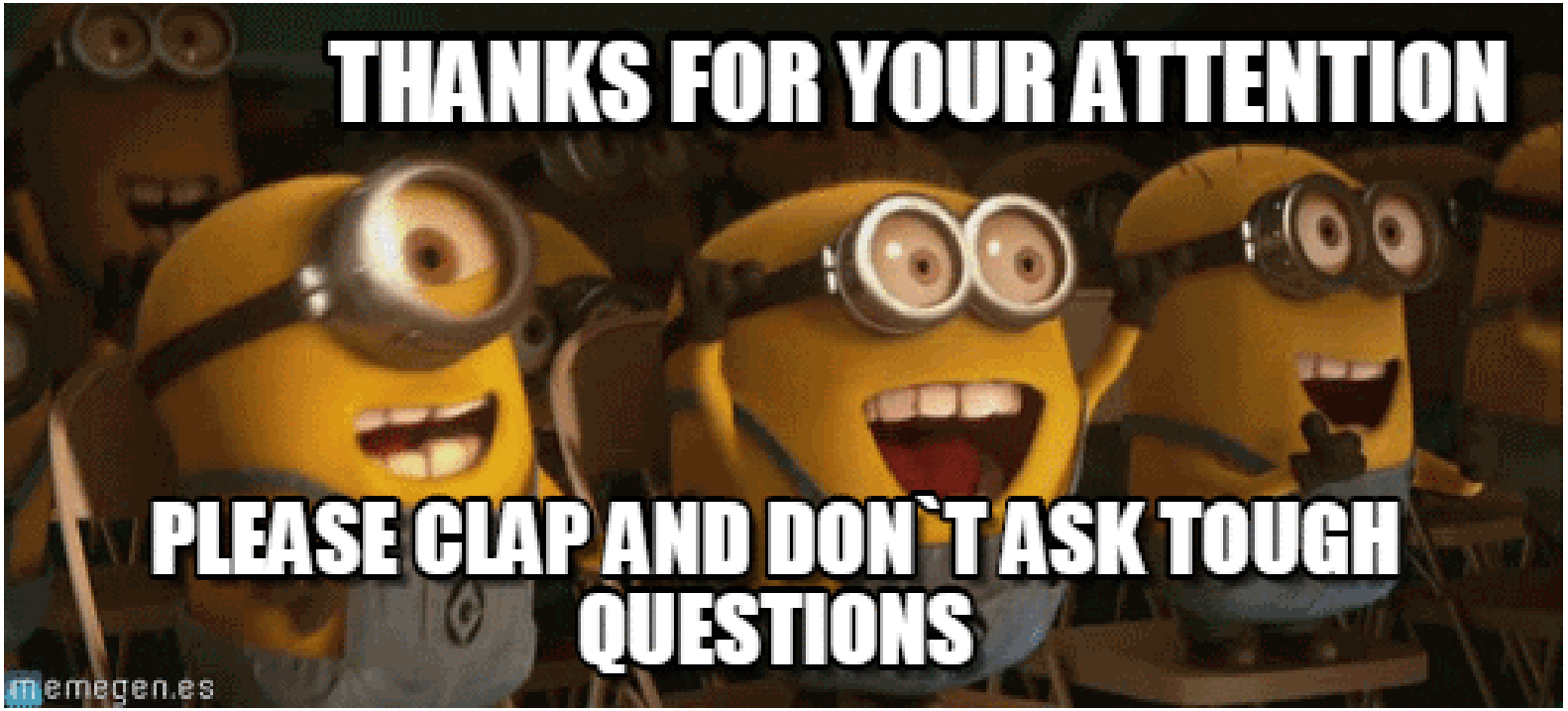

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List of Abbreviations

AMP: Auxiliary Medicinal Product

AR: Assessment Report

CEC: Coordinator Ethics Committee

CMS: Concerned Member State

CT: Clinical Trial

CTA: Clinical Trial Application

CTFG: Clinical Trial Facilitation Group

CTR: Clinical Trial Regulation

D: Day

EC: Ethics Committee

EMA: European Medicines Agency

EU: European Union

IB: Investigator's Brochure

ICF: Informed Consent Format

IMP: Investigational Medicinal Product

IMPD: Investigational Medicinal Product Dossier

MN: Multinational

P-NCA: Participating National Competent Authority

Ref-NCA: Reference National Competent Authority

RMS: Reference Member State

VHP: Voluntary Harmonization Procedure