

DIA Euroconference Monaco 9
March 2010
Session: Heads of Medicines
Agencies
HMA Initiatives on Clinical Trials

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22nd Annual
EuroMeeting
March 8-10, 2010
Monaco



Clinical Trials in Europe: what is at stake

- **Innovation in healthcare ;**
- **Providing patients with new medicines to improve coverage of medical needs ;**
- **Contribution to preserving industrial capacity in that area ;**

Clinical Trials in Europe: Europe still a significant scene but unfavourable trend

- **Still a substantial flow of clinical trials in Europe, around 5000 each year ;**
- **Among them, 75% single states clinical trials, 25% multi-states clinical trials ;**
- **But double shift:**
 - **Inside Europe, from countries with a strong pharma tradition to emerging or strengthening sites ;**
 - **From Europe to distant sites, mostly Asian, but also Latin American and African ;**
 - **Keep in mind that such shifts are to some extent natural: geographical spread of activities formerly restricted to European and North American countries is one of the drivers of economic and social progress at worldwide level ;**

Diversity of attractiveness factors in the field of clinical trials

- **Well beyond smoothness and consistency of procedures at National Competent Authorities (NCA) level ;**
- **Smooth functioning of ethics committees, which are independent from NCAs, and interaction with NCAs ;**
- **Functional infrastructures (transportation of medicines, samples...) ;**
- **Competence of investigators and Clinical Research Organizations (CROs) ;**
- **Easiness and speed of patients and healthy subjects inclusion ;**
- **Quality of operational and administrative links with health centers ;**
- **Level of costs...**

Implementation of the European regulatory framework: progress and difficulties (1/2)

- **Improved standards of quality (good clinical and manufacturing practices GCP-GMP) ;**
- **Improved communication and exchanges between members states authorities (assessors and inspectors) ;**
- **Enhanced protection safeguards for subjects ;**
- **Common technical requirements ;**
- **Progress with regard to timelines in decision-making ;**

Implementation of the European regulatory framework: progress and difficulties (2/2)

- **Persisting lack of harmonisation in some areas (requirements on CTA dossiers, a few definitions (substantial amendment, non-interventional trial...), safety reporting, IMP/NIMP concept),**
- **A few divergent decisions for multi-states EC (true but limited issue = less than 0,1 % mostly linked with clinical practice difference) ;**
- **Not enough risk-based approach to take account of the diversity in clinical trials ;**
- **Inadequate basis for multiple sponsorship,**
- **Room for progress with regard to transparency ;**

HMA reflexions and initiatives to address the remaining difficulties: the first stages

- **First discussions at HMA regular meeting in the first semester of 2007 ;**
- **Spurred by results of the 3 October 2007 European Commission/EMA workshop ;**
- **Resulting in a new mandate for CTFG (January 2008) and then an action plan (July 2008) ;**

Main orientations of CTFG new mandate and action plan 2008-2009

- **Strengthen coordination or sharing of scientific assessment of multinational clinical trials and safety data ;**
- **Harmonise processes and practices ;**
- **Develop data-sharing and information systems ;**
- **Improve communication on NCAs CT regulatory activities ;**

The achievements to date: improving coordination of assessment of multi-national CT: VHP as optional standardised procedures for multi-national CT (1/2)

- **As of Q2 2009, voluntary harmonised procedure (VHP) offers sponsors a possibility to get a clinical trial consistently approved in many members states ;**
- **With acceptable timelines (max 77 days = 7 days request for VHP + 60 days assessment + 10 days formal national application and approval) ;**
- **Pilot phase limited to multi-national CT meeting a few criteria ;**
- **A simplified clinical trial assessment (CTA) process: a single repository, same dossier, electronic submission, English accepted, a single opinion after coordinated assessment by several MS**

The achievements to date: improving coordination of assessment of multi-national CT Outcome of 2009 pilot phase and evolution of the procedure (2/2)

- Adequate timelines for assessment phase (mean around 55 days) ;
- Positive feedback from sponsors which chose to use the VHP ;
- Reluctance from other sponsors which refrained from using the VHP ;
- Adjustments decided at October 2009 HMA meeting: skipping phase 1 fixed timelines, widening the eligibility criteria, including substantial amendments for successful VHPs ;

The achievements to date: harmonisation and simplification of assessment processes and practices

- **Substantial input from CTFG on the Revised guidance on CTA, soon to be published ;**
- **A few significant moves: unified content, simplified dossiers for medicines already authorised in an ICH country (USA, Japan...), guidance for implementing notion of substantial amendment ;**

The achievements to date: developing information and work-sharing and information systems

- **Development of information sharing between NCA, with EMEA support: electronic alerts to NCAs on events concerning CTs (suspensions, temporary bricks, withdrawals of submissions for safety reasons,...) ; development of EudraCT data warehouse, meant to produce statistics or make details queries ;**
- **Operational improvements for sponsors : new functionalities to validate data entered via the Eudra CT web interface when completing CTA submission form ;**

The achievement to date: improving communication

- **Internal communication across the clinical trials regulatory network: CTFG mail box, information sharing on refusals and withdrawals, grounds for non acceptance, regular teleconferences, meetings dedicated to specific issues to build common assessment criteria, trainings on Eudravigilance ;**
- **External communications with stakeholders: invitations to CTFG meetings, public lectures on CTFG's actions and perspectives, posting on HMA website documents related to CTFG's deliverables ;**
- **Interaction with other working groups: in particular with the Commission's ad hoc expert group (one dedicated CTFG members to liaise with this group), in which several CTFG members represent their Members States), but also with other groups or committees (CHMP, Eudra CT TIG, Eudravigilance working group...);**

A lot remains to be done and could be achieved

- **Simplifying: *single repository*, avoiding “nice to know” questions, harmonising rules for Susars reporting and format for annual safety report ;**
- **Work-sharing: beyond VHP, sharing assessment of DSUR/ASR ;**
- **Adapting processes according to a risk based approach: prioritisation of NCA assessments with simplified processes for some categories of clinical trials concerning little on no risk (for example phase 4), prioritisation for safety evaluation and inspections, simplified regime for IMPD, for labeling, insurance, archiving, safety, reporting ;**
- **Need of a common approach supported by the Commission ;**

Brief overview on network cooperation in the field on clinical trial inspection (1)

Goals and Contexts

- **2 goals**

- Protection of people undergoing clinical trials
- Quality of data collected during these trials

- **2 contexts**

- Clinical trials authorised and conducted in Member States
- Clinical trials submitted in M.A. applications: conducted in E.U. Member states or in third countries

=> **2 programs usually implemented by Member States**

Brief overview on network cooperation in the field on clinical trial inspection (2)

2 programs

- **Control of national Clinical trials**

- Ongoing clinical trials and sponsor/CRO systems
- Verification of compliance with current local regulations
 - regulations on biomedical research, GCPs
 - regulations on medical and clinical practice
- Triggers :
 - Annual thematic program (i.e. 2009 : Alzheimer, Paediatrics , characteristics of product, sponsor and investigator profiles). Risk based approach
 - Complaints, informations from evaluation sector, Ethics Committee, Police

- **Clinical trials submitted in M.A. context**

- Trials included in marketing authorization applications
- Post authorization: phase IV studies, studies conducted as part of specific obligations or follow-up measures
- 2 contexts : . National – or DCP and MRP – procedures
Procedures coordinated by EMA,

Brief overview on network cooperation in the field on clinical trial inspection (3)

Cooperation between Member States

- **Control of national Clinical trials**
 - **Commission Guidances**
 - **Draft Proposal paper for better coordination and communication of inspections across EEA, (UK, S, F)**
 - **Exchange of information on completed inspections**
- **Clinical trials submitted in M.A. context (1/2)**
 - **Commission Guidance for coordination of GCP inspections and cooperation between GCP inspectors ; Context of MRP and DCP, published Dec. 2009.**
 - Designation of the reporting Inspectorate (RMS, RaP or Co-Rap in case of referrals)
 - Communication between Member States
 - Schedule for activities
 - Communication on results

Clinical trial inspection (4)

Cooperation between Member States

- **Clinical trials submitted in M.A. context (2/2)**
 - **Generic drugs**
 - Pilot guidance on selection of trials / sites to be inspected : annual risk-based programme of routine GCP inspections of the CROs most often used in the conduct of the BE trials included in M.A.A. for generic drugs. Adopted by CMDh, Dec. 2009
 - Active cooperation between M.S. inspectorates
 - Exchange of information on planned and completed inspections
 - Exchange of information on Trial sites (clinical and analytical): table continuously updated
 - Joint inspections (European Multinational Teams) : training, harmonisation, cooperation
 - Guidances :
 - Guideline on the investigation of Bioequivalence ; Draft
 - Guideline on validation on bioanalytical methods” : Published for consultation
 - Training courses for inspectors and assessors
 - Organised in 2008 by Afssaps, in 2010 by Singapore authorities + Afssaps

The revision of the 2001 directive should pave the way for further progress, building on the lessons of recent operational initiatives

- **HMA-MG response to the Commission's consultation on review of the CT directive (January 2010) ;**
- **Give robust legal ground to the MRD/DCP- like approach of the VHP ;**
- **Provide firm basis for a risk-based approach ;**

The revision of the 2001 should pave the way for further progress, solving issues that require legislative input

- **Help clarify division of labour between NCAs and ECs, to avoid duplication of work ;**
- **Strengthening safeguards to ensure compliance with GCP performed in third countries (65% of CT supporting centralized submissions at EMEA are completed there) ;**

The revision process should not stop or inhibit in 2010-2011 the search for operational and concrete improvements

- Improving information systems to facilitate work-sharing and simplification, in particular Eudra-CT and Eudravigilance CT module (example: double reporting of susars to EVCTM and NCAs could be removed as soon as EVCTM would automatically provide each NCA with the corresponding information) ;
- Updating, completing or finalizing guidance from the ad hoc experts group with CTFG contribution, to enhance consistency in interpretation ;
- Making headway to set up a European Public Registry and to allow publication of CT results via Eudra CT version 9 ;
- Identify all the operational prerequisites of a simple submission approach (clearly possible for all NCA's in EU, but what but single submission schemes involving ECs ?) ;
- Develop concrete solutions to support academic research, instead of putting it out the scope of common rules that are meant to secure safety and reliability of CT: education and training of investigators networks of investigators at EU level, reduction of IMP costs and waivers for fees,...

Conclusion

- **NCA's and HMA are fully aware of the stakes and keen to foster further operational improvements ;**
- **Progress has recently been achieved, and there is still room for concrete moves within the current legal framework ;**
- **A revision of the directive may bring added value to solve pending issues and give firm basis to innovation ;**
- **Coordination and simplification should be further pursued without weakening protection of subjects nor undermining quality of data.**