Has the Voluntary Harmonisation Procedure (VHP) been a successful attempt to streamline the approval process for multinational clinical trials in the EU?

Examining applicants' experience to date with the Clinical Trials Facilitation Group's initiative.

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Current Legal Framework

- EU clinical trials are regulated by the Clinical Trials Directive
- Released in 2001, its provisions were transposed into the national legislation of all EU Member States (MS) by May 2004
- Prior to the Directive, varying regulation across the EU meant delays and complications detrimental to the effective conduct of trials
- The Directive sought to resolve these issues by introducing a set of harmonised requirements
  - 'Clinical Trial Authorisation'

Issues

- Differing interpretations of the Directive by MS during national implementation
  - varying submission requirements
  - requests for additional documents
- Differing philosophies and assessment techniques result in diverging opinions on common documentation
- Impact on regulatory burden, timelines, costs, and potentially the scientific value of study data
- Impact on attractiveness of the EU as a clinical research environment
  - 25% decline 2007-2011[2]

Importance of Trials

- Clinical trials are crucial for the development of existing and innovative medicines
- Also a key contributor to growth and jobs with significant levels of research and investment in the EU (approx. €20 billion per year)[1]
- Current lack of harmonisation particularly impacts multinational clinical trials (trials in more than one MS)
- Multinational clinical trials currently represent 24% of all EU clinical trials, but this equates to 67% of all trial participants[2] (growing)

The VHP

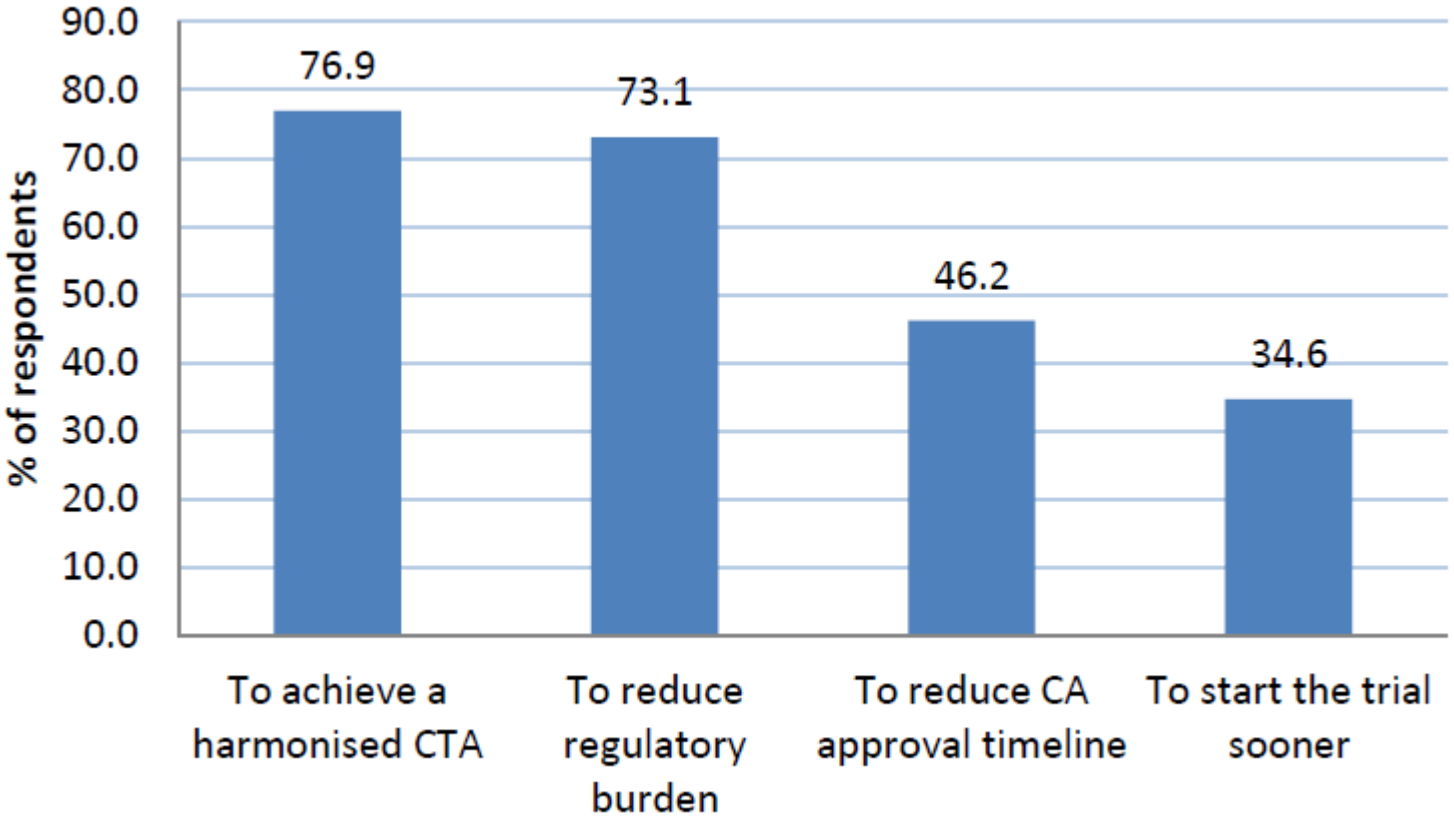
- The Clinical Trials Facilitation Group (CTFG) was established by the Heads of Medicines Agencies (HMA) in 2004 to coordinate the implementation of the Directive across EU MS
- CTFG saw the need to harmonise multinational trials, by means of harmonising NCAs' processes and practices, as a priority
- The voluntary harmonisation procedure (VHP) was introduced by the CTFG in 2009, updated 2010
- In a nutshell, the VHP allows central CTA submission and coordinated assessment of a core package of trial documents, followed by a short national CA approval step

My Research

- After 3 years in existence, the VHP had been used approx. 200 times (~6% of MN-CTs)
- Looked to investigate applicants' experience of the VHP
- Sent questionnaire to regulatory affairs professionals involved CTA submissions
- Questions designed to ascertain what issues were most important to applicants, and whether these had been addressed by the VHP

My Research Findings

Reasons applicants gave for utilising the VHP



My Research Findings

Positives

- Low incidence of divergent decisions
  - 88.9% indicated that there were no divergent decisions or, if they were, these were resolved during the VHP
- Reduced regulatory burden
  - 74.4% felt that the VHP reduced the regulatory burden associated with obtaining CTAs
- Reduced timelines to CTA in all participating MS
  - Particularly true where many MS are involved in the trial

My Research Findings

Negatives

- Tight and inflexible timelines
  - e.g. 10 days to respond to GNA after assessment step I
- Lack of adherence to timelines
  - National step taking longer than 10 days in some MS
- Some national approvals faster
  - e.g. Belgium
- Also, some MS opting out, no inclusion of EC review, lack of opportunity to discuss misunderstandings, lack of transparency…

My Research Findings

Overall

- The VHP offers greatest advantage where
  - Many MS involved
  - Divergent opinions are anticipated
  - National documentation not immediately available

- Some instances where national process preferable
  - Depends on objectives and countries involved

New Regulation

- The European Commission is proposing a new Regulation governing Clinical Trials (2016)
- Learnings from applicants' experiences with the VHP?
- Key to the success is likely to be the new approval process - distinction made between aspects where
  - MS will cooperate (Part I)
  - MS conduct their review individually (Part II)
- Distinction made without prejudice as to the body that performs the assessment (i.e. ECs and CAs)

New Regulation

Applicants' comments	Commission's proposal
Mandatory use by all EU MS	Participation will be mandatory.
Greater compliance by NCA	Compliance should be ensured through the direct applicability of the Regulation across the EU. Furthermore, clear timelines, tacit authorisations, and the Commission's ability to 'perform controls in Member States' should contribute to improved compliance.
Incorporation of CEC review	This has partially been resolved. Responsibilities of the NCA and CEC are not defined in the proposed Regulation as they were in Directive 2001/20/EC. MS must define the organisational setup and internal competences for assessing clinical trials, resulting in a single opinion within the given timelines.

New Regulation

Applicants' comments	Commission's proposal
Simplify the addition of new countries	Submission to new countries through EU portal, with set timelines for responses on Part I and Part II of the Assessment Report. So called 'additional MS concerned' must agree with rMS conclusions on Part I of the Assessment Report except in certain, well-defined cases.
Opportunity for discussion	Unclear what level of communication will be possible, but should be able to discuss issues with the rMS (communication is directly with the rMS through the EU portal) for issues related to Part I of the assessment report and individual MS for issues related to Part II.
Faster review process with greater flexibility	Standard review timelines are reduced, with opportunities for limited extensions where additional time is needed.

New Regulation

Applicants' comments	Commission's proposal
Increase transparency	There will be a clear process for appointing a 'reporting MS'. Should also be clear which MS are raising which issues.
Reduce fees	Impact on fees is unclear, but MS must levy a single fee regardless of the number of bodies making the assessment.
Single submission	Single electronic submission will be made through an EU portal.
Risk-based approach	Review timelines will be significantly shorter for so called 'low-intervention' trials.

Implications

- Outlook positive for applicants of MN-CTs whose main concerns appear to have been addressed in the new Centralised Approval Procedure (what about single country trials?)
- Positive future for MN-CTs in the EU with a harmonised and coordinated review process
- Until 2016, applicants will continue to rely on the existing national routes or opt to use the VHP

References

1. Commissioner Dalli delivers speech on "Clinical Trials Directive – Meeting Patients' Needs". Joint EFPIA/Roche event, 7 March 2012. Available from: URL: http://ec.europa.eu/commission_2010-2014/dalli/docs/speech_07032012_en.pdf
2. Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. European Commission, 17 July 2012. Available from: URL: http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf

Questions?