Navigating the Transition from Voluntary to Mandatory Harmonization Procedure: Real World Case Study

New EU Clinical Trials Regulation
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October 2015
Disclaimer

The opinions expressed are my own and not necessarily the opinions of Janssen Research and Development, LLC, or any other organization or individual.
Presentation overview

• Compare and contrast VHP expectations versus realities
• Examine lessons learned to optimize regulatory strategies without negatively affecting timelines
• Learn to work with a CRO partner in executing CTA strategies
• Develop strategies to move procedures from VHP to MHP
Case Background

• Minimum organizational experience with VHP
• Highly competitive development class
• Global clinical development plan
  – Four Phase 3 studies
• Leveraged CRO experience in clinical trial execution
• Ultimate question posed to regulatory and clinical teams: To VHP or not VHP?
VHP has been enlarged in the number of initial applications, substantial amendments and distribution of Sponsors (worldwide: EU; USA, Canada, Australia, Singapore).
To VHP or not VHP - Strategic perspective

• Strategic considerations
  – Experience with procedure
  – No clear understanding of the procedure
  – Timeline implications
  – Harmonized approach

• CRO partnership considerations
Why partner with a CRO?

- Accelerate business growth
- Access critical capabilities
- Build critical mass
- Accelerate R&D
- Reduce costs and capacity
Potential CRO/Pharma partnership pitfalls

- Poor communication
- Poorly negotiated terms
- Poorly defined partner roles
- Ineffective alliance leadership / governance
- Weak internal and external commitment
- Cultural differences
- Senior Management changes
CRO partnership leadership / governance

• A common model calls for the formation of a joint development team (JDT) to manage the project / program
• There may be discipline-based subteams that manage operational activities
• Each party will usually assign someone to serve as the “point of contact”
• There is usually a joint steering committee to oversee the budget and resolve major conflicts
Roles and responsibilities

- Should be clearly defined from the start
- Each side should focus on what they are best at
  - Keep in mind the partner's drivers, culture, and operating environment
- Ability of sub-teams to reach a common ground has a major impact on the success partnering of the JDT as a whole
To VHP or not VHP-Historical perspective

• Changes in the regulatory and clinical trial landscape
  – The Clinical Trials Directive 2001/20/EC aimed to harmonize the conduct of clinical trials within EU Member States (MS)
    • Implementation was not ideal due to different national practices
    • Lack of CA harmonization on decisions and timelines
    • Challenge for Ethics Committees and Sponsors
To VHP or not VHP-Historical perspective

- Clinical Trials Facilitation Group (CTFG) coordinated implementation of the EU CT Directive
  - CTFG facilitated a voluntary harmonization procedure (VHP) for the assessment of multinational clinical trials
  - Pilot phase carried out in 2009 and further refined
  - Repealed Directive 2001/20/EC
  - Entered into force on 16 June 2014; in effect not earlier than 28 May 2016
To VHP or not VHP

• Decision to pursue VHP made on the grounds:
  – Benefits of harmonized CTA filings
  – Opportunity to shape the regulatory environment
  – Experience of CRO partner

• Total of four Phase III studies
  – Two studies initially submitted to obtain experience and learnings (Study 1 & 2; VHP 1)
  – Two additional studies submitted subsequently (Study 3 & 4; VHP 2)
Basics of VHP procedure

• Three phase process
  – Phase 1: Request for VHP and validation of the application
  – Phase 2: Assessment step:
    • Review of a CTA by the NCAs participating in VHP
  – Phase 3: National step
    • Formal CTAs submitted to all concerned NCAs
# Basics of VHP procedure

<table>
<thead>
<tr>
<th>Step 1: Request for a VHP</th>
<th>Step 2: VHP Assessment</th>
<th>Step 3: National Step</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validation</td>
<td>Assessment</td>
<td>Formal CTA</td>
</tr>
</tbody>
</table>

5 working days

- Cover letter
- Core CTA EudraCT form
- Protocol
- IB
- IMP dossier
- IMP certificates
- NIMP dossier
- Copy of SA

32 or 60 calendar days

- Day 32- Approval
  - OR
  - GNA
- Day 42-Response to VHP coordinator
- Day 42-60-VHP assessment (Step II)
- Day 56-Approval OR Questions
- Day 60-Approval upon resolution of issues OR No approval
- Resubmission through VHP or national CTA

- Submission within 20 calendar days after VHP approval
- CA approval within 10 days
- No scientific discussion on the agreed documents of the VHP (e.g. Protocol, IB, IMPD)
- Additional documentation e.g.
  - Patient facing materials
  - Investigator information
  - Site contracts
  - Insurance
Considerations of VHP procedure

• Clinical trials involving 2 or more MS are eligible to participate in the VHP
• Sponsor nominates list of countries
  – CA can opt out of procedure
  – Some CA historically do not participate in VHP
    • E.g. Slovakia, Slovenia, Luxembourg
• Addition of new countries possible after all 3 Phases of VHP complete
  – Number of new countries restricted to not more than in first VHP
  – Justification should be provided
Considerations of VHP procedure

- **Substantial amendments permitted**
  - After all CA approvals received
  - Validation (5 calendar days)
  - Response for requests (3 working days)
  - Action on substantial amendment (35 working days after validation)
    - Questions can be received on Day 21; Responses Day 24
  - Process can take up to 53 working days
- **Positive VHP opinion**
  - Submit to CA within 10 working days
  - CA approval within 7 working days after validation
What really happened
### What really happened - Submissions

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries identified</th>
<th>Submission date</th>
<th>Day when validation completed</th>
<th>Countries accepted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>CZ, FR, DE PEI, HU, ES, UK, IT, PL, RO and SE</td>
<td>14-Nov-14</td>
<td>24-Nov-14</td>
<td>CZ, FR, DE PEI, HU, ES, UK NON-VHP: IT, PL, RO and SE</td>
</tr>
<tr>
<td>Study 2</td>
<td>AT, BE, CZ, FR, NL, ES, UK, PL, RO</td>
<td>17-Nov-2014</td>
<td>26-Nov-2014</td>
<td>AT, BE, CZ, FR, NL, ES, UK NON-VHP: PL, RO</td>
</tr>
<tr>
<td>Study 3</td>
<td>DE, PL, ES, UK</td>
<td>9-Mar-15</td>
<td>16-Mar-15</td>
<td>All</td>
</tr>
<tr>
<td>Study 4</td>
<td>DE, HU, PL, UK</td>
<td>9-Mar-15</td>
<td>16-Mar-15</td>
<td>All</td>
</tr>
</tbody>
</table>

- All studies had validation periods longer than 5 working days
What really happened – Queries

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of deficiencies received on Day 32 per each Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>27 questions Clinical-8 Quality-13 Statistical-6</td>
</tr>
<tr>
<td>Study 2</td>
<td>21 questions Clinical-7 Quality-14</td>
</tr>
<tr>
<td>Study 3</td>
<td>2 questions Clinical-1 Quality-1</td>
</tr>
<tr>
<td>Study 4</td>
<td>4 questions Clinical-3 Quality-1</td>
</tr>
</tbody>
</table>

Reminder: Responses submitted between Day 32 - Day 42 – 10 days is a very short time!
Clinical Trial Application (CTA) Submissions and Approvals-VHP (Phase 1 & 2)

VHP-1 Approval
Feb 6
Nov 14 - Feb 6
85 days

VHP-2 Approval
May 12
Mar 9 - May 12
65 days

VHP-1 (Study 1/Study 2)

VHP-2 (Study 3/Study 4)
VHP-1 CTA Status
Submission to Approval Timeline

Legend:
- Study 1
- Study 2

VHP-1 Approval
Feb 6

2015

France
- Feb 25 - Feb 27
- 17 days
- Feb 25 - Mar 13
- 20 days
- Feb 25 - Mar 16

UK
- Feb 25 - Mar 13
- 17 days
- Feb 25 - Mar 23
- 27 days
- Feb 25 - Mar 19

Germany
- Feb 25 - Mar 16
- 20 days
- Feb 25 - Mar 23
- 27 days
- Feb 25 - Mar 19

Spain
- Feb 25 - Jul 6
- 132 days
- Feb 26 - Jun 24
- 119 days
- Feb 26 - Jun 24

Czech Republic
- Feb 26 - Mar 19
- 22 days
- Mar 13 - Apr 1
- 20 days
- Mar 27 - Apr 14

Belgium
- Mar 10 - Apr 24
- 46 days
- Mar 13 - Apr 1
- 20 days
- Mar 27 - Apr 14

France
- Apr 10 - Apr 17
- 8 days
- Apr 10 - Apr 17
- 19 days
- Apr 10 - Apr 17

Netherlands
- May 21 - Jul 27
- 68 days

Legend:
- Study 1
- Study 2
VHP-2 CTA Status Submission to Approvals Timeline

Legend:
- Study 3
- Study 4

2015

<table>
<thead>
<tr>
<th>Country</th>
<th>Study 3 Approval Dates</th>
<th>Study 4 Approval Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hungary</td>
<td>May 14 - May 22</td>
<td>Aug 24 - Aug 28</td>
</tr>
<tr>
<td>Poland</td>
<td>9 days</td>
<td>88 days</td>
</tr>
<tr>
<td>Germany</td>
<td>May 14 - May 20</td>
<td>Jun 2 - Aug 28</td>
</tr>
<tr>
<td>UK</td>
<td>7 days</td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td></td>
<td>100 days</td>
</tr>
<tr>
<td>Spain</td>
<td>30 days</td>
<td>May 21 - Jun 19</td>
</tr>
<tr>
<td>Germany</td>
<td>9 days</td>
<td>May 14 - May 22</td>
</tr>
<tr>
<td>UK</td>
<td>9 days</td>
<td>May 14 - May 22</td>
</tr>
</tbody>
</table>
Key observations in CTA process

• ECs have a more significant role in approval process
  – Questions on study design
• Pay attention to ICF wording
  – General language vs. country specific language
• CA may differ in opinion from ECs (Austria, Italy)
• Some CA (e.g. Poland may offer a silent approval)
• Additional national requirements
  – BfS approval (Germany)- 8-10 months
  – Trial registry information posting (Spain)
  – Submission to same portal for CA/EC review (Italy)
VHP Best Practices & Lessons Learned

• Meetings with CRO-frequency/planning
  – Kick-off meeting
  – Weekly teleconferences
  – Ad-hoc communication

• Operational planning between VHP phases
  – Prepare national submissions while waiting for VHP approval

• Availability and translation of external to regulatory documents
  – i.e. patient facing materials, contracts, translations, national coordinators
VHP Best Practices & Lessons Learned

• Communication
  – Identify processes for communication early on, taking geographical challenges, language barriers, and time differences into account
  – EVERYTHING related to a problem / issue should go through a single point of contact and be communicated early
  – Within company functions, with the CRO, within the CRO
    • Alignment on understanding of goals/timelines
    • Submission tracking and archiving

• RA strategy responsibility remains with company
  – Ensure no decisions with impact on CTA submission done without regulatory approval
VHP Best Practices & Lessons Learned

• Challenge the timelines and be ready for the earliest possible submission
• Ensure key team members are available during response period(s)
Transition to the MHP

- Regulation takes effect not earlier than 28 May 2016
- EMA to set up clinical trial database and submission portal
  - Submission of a single CTA
- Two part review process
- Part I:
  - Submission of core documents (IMPD, protocol, IB, etc.)
  - RMS to assess CTA for validity and scientific merit, as well as therapeutic benefit, and ensuring safety to subjects
  - RMS to draft an assessment report based on review findings
  - Report to be distributed to all concerned EU member states for review
  - Report will be applicable in all EU member states
    - Member states may not agree with the conclusions of the RMS
Transition to the MHP

• Reasons for Member States disagreement
  – (a) when it considers that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State
  – (b) infringement of its national law under Article 90 (e.g. clinical studies of prohibited or restricted materials such as human or animal cells or medicinal products containing or derived from human or animal cells, abortion inducing drugs, or narcotics)
  – (c) reservations regarding subject safety or data reliability and robustness
Transition to the MHP

• Part II: EU member states will assess the application based on their national and ethical requirements relating to trial conduct

• Each member state will determine:
  – The makeup of its Ethics Committee
  – Organize the review process
  – Requirements for informed consent
  – Compensation of subjects and investigators
  – Insurance
  – Site/Investigator issues (e.g. storage of biological samples)

• Part II can be submitted with Part I or after Part I approval
  – Submitted within 2 years of Part I approval
  – Availability and timing of national documents will be essential
Transition to the MHP - Keys to success

- Adherence to timeline will be essential
  - Response to queries limited to 12 days
- Clear understanding of roles and responsibilities
  - Internally and externally
- Communication processes paramount
- Alignment on process and operational execution
- Availability of key personnel/decision makers
Thank you