Risk-Based Approach to Clinical Trial Legislation – Improvement options in the current and new legislation

Beat Widler, PhD, dipl. pharm. med., Clinical QA & Risk Management Expert
Widler & Schiemann Ltd., Zug – Switzerland

10.10.2011, Basel / Switzerland
Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. (“DIA”), its directors, officers, employees, volunteers, members, chapters, councils, Special Interest Area Communities or affiliates, or any organization with which the presenter is employed or affiliated.

These PowerPoint slides are the intellectual property of the individual presenter and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved. Drug Information Association, DIA and DIA logo are registered trademarks or trademarks of Drug Information Association Inc. All other trademarks are the property of their respective owners.
What is the starting point?

- Europe – Clinical Trials Directive et al.
- USA – CFR and Guidelines
- Globally – ICH GCP et al.
What is going on?

- Europe - EMA
- USA – FDA
- UK - MHRA
- Globally
What is going on?
Europe - EMA

Compliance & Inspection Reflection Paper on Risk based Quality Management in Clinical Trials

4 August 2011 EMA/INS/GCP/394194/2011
What has already been achieved

- Principles of ICH Q8 Pharmaceutical Development
- ICH Q9 Quality Risk Management
- ICH Q10 Pharmaceutical Quality System

Simply advocating the “highest level” of quality has little practical meaning in itself
EMA Compliance & Inspection Reflection
Paper

Strategic Considerations

• Key elements of the quality system:
  • Documented procedures developed, implemented & kept up-to-date
  • Training
    • sponsor personnel
    • partners
    • trial sites
  • Validation of computerized systems
  • Monitoring of trial sites and technical facilities
    • on-site
    • centralized monitoring techniques
  • Data management & quality control
  • Internal & external audits by independent auditors
What is going on?
Non-governmental Activities
but endorsed / recognized by Regulators

• ADAMON
• ECRIN
• OPTIMON
• OECD (Organization for Economic Co-operation and Development)
• CTTI (Clinical Trial Transformation Initiative)
  • a public – private partnership

• CTFG
• GCP IWG
What is going on?

US FDA

Guidance for Industry

Oversight of Clinical Investigations

A Risk-Based Approach to Monitoring
US FDA
Key Messages

• Focus on the processes critical to
  • protecting human subjects
  • maintaining the integrity of study data
  • compliance with applicable regulations

• Monitoring / Audit findings used to
  • correct inadequate investigator & site practices regarding
    - human subject protection
    - poor data quality
US FDA
Revisiting “old” Positions

FDA withdraws guidance on monitoring of clinical investigations of 1988

the “most effective way” to monitor an investigation is to “maintain personal contact between the monitor and the investigator throughout the clinical investigation.”
US FDA
A new Paradigm emerges

• Abandon a “no error approach”
• “A low, but non-zero rate of errors in capturing certain baseline characteristics of enrolled subjects (e.g., age, concomitant treatment, or concomitant illness) will not, in general, have a significant effect on study results”
• “In contrast, a small number of errors related to study endpoints (e.g., not following protocol-specified definitions) can profoundly affect study results, as could failure to report rare but important adverse events”
US FDA

Components of the new Paradigm

• Complexity of the study design
• Types of study endpoints
• Clinical complexity of the study population
• Geography
• Relative experience of the clinical investigator and of the sponsor with the investigator
MHRA on Risk Adaptation, 1 April 2011

- 15 notifications submitted for type A trials, 7 eligible
- Risk adaptation more than monitoring (but first aspect tackled by the MHRA)
- More guidance in future FAQs
- Changes to the GCP guide
MHRA

• Inspectors trained to consistent views of the risk adaptation model

• “Risk Adaptation Collaborative Group”
  • discuss approaches used in the past
  • design the FAQs and sample tools

• Revise or addenda to ICH E6 in order to allow for risk adaptation?

• Guidance on risk-proportionate approaches to the management & monitoring of clinical trials
MHRA

Guidance purpose assist investigators & sponsors:

• Consider & identify the main hazards inherent in a clinical trial protocol
• Develop relevant risk-mitigation plans
• Develop proportionate trial management & monitoring plans.
• Assessment of risks to the safety & rights of the trial participants
• Risks to the reliability of the trial results associated with the design, data collection, analysis
MHRA

*Does not address risks associated with the training & experience of the trial team, host sites or other institutions involved in the conduct of a study*

Points to consider in developing a safety monitoring plan:

- Nature of the IMP
- Potential toxicities (known/unknown) i.e. hazards
- Body systems possibly affected
- Type of monitoring / mitigation
MHRA
Take Home Messages

The more robust the design the less the dependence there is on quality control and assurance measures to secure reliable results

A key word used is “Simple”

Important to recognise that it is the reliability of the trial results rather than the data per se that is paramount
MRC/DH/MHRA Joint Project

Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products of March 2011
MRC/DH/MHRA Joint Project

• Brosteaunu and colleagues in the ADAMON Project:

• Type A = No higher than the risk of standard medical care ➔ low intensity of safety monitoring
• Type B = Somewhat higher than the risk of standard medical care ➔ moderate intensity
• Type C = Markedly higher than the risk of standard medical ➔ high intensity above standard of care
MRC/DH/MHRA Joint Project

- Protocol states
  - certain adverse events not reported by the investigator to the sponsor in the normal way
  - proposal in the protocol assessed at the time of the CTA assessment by the MHRA
- Applies to Type A trials & potentially some Type B trials
Quality by Design (QbD)

What needs to change?
How do Sponsors need to change?
All quality and compliance efforts are geared at ensuring

1. Patients’ safety & integrity + protection of their rights
2. Integrity of data collected in a trial to avoid false rejection or acceptance of the study hypothesis
3. Compliance with the law & Regulations
4. Acceptance of deviations / non-conformities that do not impact on the above 3 objectives
Quality by Design (QbD)

What needs to change?
How do Sponsors need to change?

5. A strict & predefined planning process followed when developing a protocol and setting up the trial
6. A suite of meaningful and objective KRI and KPI is used to measure quality performance
7. Objective criteria are developed to trigger on-site monitoring or audit activities, respectively
Quality by Design (QbD)

What needs to change?
How do Sponsors need to change?

8. On site monitoring activities
   • serve to enrich the inference on quality & compliance provided by the centralized analysis of KRI & KPI data
   • verify & “validate” the inference made through the centralized review, and, if the inference is wrong initiate CAPAs
Quality by Design (QbD)

What needs to change?
How do Sponsors need to change?

9. Audits serve the purpose described in item 8) & in addition will test through appropriate audit techniques the robustness of the QMS

10. Standards developed in groups such as CTTI are not modified unless there is an objective reason, and then rationale and type of change are shared with the Standard custodian(s).
## Contact me

<table>
<thead>
<tr>
<th>Name</th>
<th>Tel office:</th>
<th>Mobile:</th>
<th>Fax:</th>
<th>e-mail:</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beat E. Widler PhD</td>
<td>+41 79 321 7 321</td>
<td>+41 79 321 7 321</td>
<td>+41 61 312 70 43</td>
<td><a href="mailto:widler.ed@gmx.ch">widler.ed@gmx.ch</a></td>
<td><a href="http://www.wsqms.ch">www.wsqms.ch</a></td>
</tr>
<tr>
<td>ETH-Z</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Managing Partner</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widler &amp; Schiemann</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weinberghöhe 10 B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH 6300 Zug</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>