Regulatory Requirements

CTTI Quality by Design Workshop 28-29 Jan 2013
Rockville, MD
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European Medicines Agency
Disclaimer

The views presented in this presentation/these slides are those of the author and should not be understood or quoted as being made on behalf of the EMA and/or its scientific committees.
Regulatory Requirements and guidelines for quality of design

- Directive 2001/83/EC Annex 1
- Directive 2001/20/EC and directive 2005/28/EC
- General guidelines – GCP, Statistical analysis, Clinical study report, Clinical trials in paediatric or elderly populations
- Guidelines on clinical development of medicinal products in specific therapeutic areas
- Scientific advice (non-binding) – optional possibility for sponsor to seek scientific advice on the development of a medicine - clinical, pre-clinical, pharmaceutical
Regulatory requirements for clinical trial design

- Legislation is general – broad principles.
- More information is in guidance – but it still offers considerable flexibility.
- Guidance leaves much to be defined by the sponsor in their policies, processes and procedures. Better alternatives can be justified case by case.
- The detail or complexity of trial conduct is driven by established practice, perceived requirements, “the oral and written culture” which is very open to change. Many of the issues lie in this “cultural” category as do the obstacles to change.
Defining Quality

Quality sufficient to support the decision making process on medicines throughout the clinical development and use post-marketing authorisation.

Collecting data, generating information, enabling decision making by:

- Sponsors
- Ethics Committees
- Regulators
- Investigators
- Healthcare professionals
- Study subjects
- Patients

Ensuring:
- Subject rights, safety and welfare
- Robustness of data
Current Developments
Current developments – helping to make that flexibility clear and put into practice

- EU GCP IWG/CTFG draft Reflection paper on risk based quality management – to finalize this year

- OECD Recommendation on risk based approach endorsed – finalized – publication anticipated soon once endorsed by OECD Council

- FDA Draft guidance on monitoring

- EU GCP IWG / CHMP “Points to consider on GCP inspection findings and the benefit-risk balance” Final – publication in coming weeks

- EU Draft regulation on clinical trials
Points to consider on GCP inspection findings and the benefit-risk balance

<table>
<thead>
<tr>
<th>Points</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agreed by GCP IWG</td>
<td>&lt;Month YYYYY&gt;</td>
</tr>
<tr>
<td>Adopted by CHMP</td>
<td>&lt;DD Month YYYYY&gt;³</td>
</tr>
<tr>
<td>Date for coming into effect</td>
<td>&lt;DD Month YYYYY&gt;¹</td>
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</table>
“Points to consider on GCP inspection findings and the benefit-risk balance”

• Agreed by GCP IWG, adopted by CHMP November 2012. Publication in process.

• It is a Discussion paper on key GCP inspection issues impacting risk / benefit considerations by CHMP.

• Objective - to assist inspectors and assessors in evaluating the consequences of inspection findings in relation to the benefit-risk balance. Building prioritisation and risk assessment into conclusions and decisions based on inspection.

• Three categories are used:
  – Inspection findings which are likely to influence the benefit-risk evaluation
  – Inspection findings which may influence the benefit-risk evaluation
  – Inspection findings which are less likely to influence the benefit-risk evaluation
Introduction

- Many non-compliances may result in increased variability/reduced precision
- May blur real differences between treatment groups
- For superiority studies, if superiority has been established, non-compliances which increase variability, but not introducing bias favouring one treatment over the other are relatively unproblematic
- For non-inferiority studies. Increased variability may disguise a real difference between products. On the other hand, increased variability tends to widen the confidence interval for the mean difference/ratio between the test and comparator making the non-inferiority claim more difficult to obtain.
- Non-compliance in the intermediate and low-impact category may not affect the benefit-risk assessment looked upon in isolation.
- Major ethical flaws have an impact on the final conclusions about approvability of an application. Consequently, ethical misconduct could result in rejection of the application.
OECD Global Science Forum

Facilitating International Cooperation in Non-Commercial Clinical Trials

OCTOBER 2011

Final Version Agreed and publication imminent
Reflection paper on risk based quality management in clinical trials
Draft

<table>
<thead>
<tr>
<th>Draft Agreed by the CTFG for release for consultation</th>
<th>31 May 2011</th>
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<tbody>
<tr>
<td>Draft Adopted by the GCP Inspectors Working Group for consultation</td>
<td>14 June 2011</td>
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<tr>
<td>End of Consultation (Deadline for Comments)</td>
<td>15 February 2012</td>
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</table>
Guidance for Industry
Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.
Mission and objectives

The European Clinical Research Infrastructures Network, www.ecrin.org, is a European network dedicated to improving the health of patients and citizens across the world through clinical research.

ECRIN supports, services, coordinates, and manages high-quality, independent, and fully transparent multinational clinical research. ECRIN synergizes the capacities and capabilities of national clinical research. ECRIN strives for harmonisation of European clinical research.

By facilitating clinical research across Europe, ECRIN contributes to the achievement of the 'European Research Area' and the 'society of knowledge' and adds to European competitiveness.
Brussels, 17.7.2012
COM(2012) 369 final
2012/0192 (COD)

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
Draft regulation on clinical trials.
for co-decision by Council and Parliament

• Single dossier, single application portal for EU, encompassing regulatory and ethics review.

• Joint assessment of core information Part 1 between involved member states and national assessment of Part 2. Single decision per trial and per member state.

• Low intervention trials – marketed product within SPC or established medical practice – rapid assessment, dossier is simple, additional labeling only if required by study design.

• Emergency treatment trials

• Insurance, labeling

• Improved framework for safety reporting
Some data from inspection findings
Number of EMA/CHMP requested inspections conducted by region and year (2000-2011)
Number of findings by grading (2000-2010)
GCP inspections requested by EMA  2000-2012
Monitoring findings

All GCP inspections requested by EMA databased – each inspection finding coded and entered:

- grading
- related GCP requirement
- verbatim text of finding statement but not supporting narrative which is in report
- activity
- responsibility
# Number of findings per sub-category of the top 3 main categories (general, investigational site and trial management) graded by critical, major and minor - GCP IWG annual report 2011 – GCP inspections requested by EMA

<table>
<thead>
<tr>
<th>Deficiency Category Name</th>
<th>Deficiency Sub Category Name</th>
<th>Critical</th>
<th>Major</th>
<th>Minor</th>
<th>Total</th>
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<tbody>
<tr>
<td>General</td>
<td>Contracts/Agreements</td>
<td>1</td>
<td>2</td>
<td>7</td>
<td>10</td>
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<td></td>
<td>Direct Access to Data</td>
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<td></td>
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<td></td>
<td>Essential Documents</td>
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<td>15</td>
<td>50</td>
<td>68</td>
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<tr>
<td></td>
<td>Facilities and Equipment</td>
<td>5</td>
<td>6</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Organisation and Personnel</td>
<td>7</td>
<td>18</td>
<td></td>
<td>25</td>
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<tr>
<td></td>
<td>Qualification/Training</td>
<td>2</td>
<td>10</td>
<td>20</td>
<td>32</td>
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<td></td>
<td>Randomization/Blinding/Codes IMP</td>
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<td></td>
<td>1</td>
<td>1</td>
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<td></td>
<td>SOPs</td>
<td>19</td>
<td>21</td>
<td></td>
<td>40</td>
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<td></td>
<td>Source Documentation</td>
<td>1</td>
<td>18</td>
<td>18</td>
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<td><strong>General Total</strong></td>
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<td><strong>7</strong></td>
<td><strong>78</strong></td>
<td><strong>141</strong></td>
<td><strong>226</strong></td>
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<tr>
<td>Investigational Site</td>
<td>Protocol Compliance (Assessment of Efficacy)</td>
<td>4</td>
<td>4</td>
<td></td>
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<tr>
<td>----------------------</td>
<td>---------------------------------------------</td>
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<td></td>
<td></td>
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<tr>
<td>Protocol Compliance (Others)</td>
<td>1</td>
<td>11</td>
<td>15</td>
<td>27</td>
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<tr>
<td>Protocol Compliance (Safety Reporting)</td>
<td>8</td>
<td>9</td>
<td>17</td>
<td></td>
<td></td>
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<tr>
<td>Protocol Compliance (Selection Criteria)</td>
<td>10</td>
<td>4</td>
<td>14</td>
<td></td>
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<tr>
<td>Reporting in CRF/Diary</td>
<td>1</td>
<td>14</td>
<td>37</td>
<td>52</td>
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<tr>
<td><strong>Investigational Site Total</strong></td>
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<td><strong>47</strong></td>
<td><strong>65</strong></td>
<td><strong>114</strong></td>
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Number of findings per sub-category of the top 3 main categories (general, investigational site and trial management) graded by critical, major and minor - GCP IWG annual report 2011 - GCP inspections requested by EMA

<table>
<thead>
<tr>
<th>Trial Management (Sponsor)</th>
<th>Audit</th>
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<th></th>
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<tbody>
<tr>
<td>CSR</td>
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<td>2</td>
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<tr>
<td>Data Management</td>
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<td>Document Control</td>
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<td>19</td>
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<tr>
<td>Monitoring</td>
<td>3</td>
<td>15</td>
<td>17</td>
<td>35</td>
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<tr>
<td>Protocol/CRF/Diary/Questionnaires design</td>
<td>6</td>
<td>3</td>
<td>9</td>
<td></td>
<td></td>
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<tr>
<td><strong>Trial Management (Sponsor) Total</strong></td>
<td><strong>10</strong></td>
<td><strong>55</strong></td>
<td><strong>49</strong></td>
<td><strong>114</strong></td>
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</table>
GCP inspections requested by EMA 2000-2012 Monitoring findings

Critical  45
Major     145
Minor     87
Total     277
Analysis

- Based on verbatim finding only
- Review of supporting evidence not yet included
- Some items “insufficient monitoring” are further detailed in the report but not in the database – need more investigation
- Minor findings not reviewed
GCP inspections requested by EMA 2000-2012

Monitoring findings

<table>
<thead>
<tr>
<th>Finding type</th>
<th>Critical</th>
<th>Major</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor did not report/act on problems</td>
<td>8</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>Deficient SDV</td>
<td>9</td>
<td>15</td>
<td>24</td>
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<tr>
<td>Insufficient Monitoring</td>
<td>5</td>
<td>34</td>
<td>39</td>
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<tr>
<td>No action by sponsor</td>
<td>7</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Failure to visit lab or other technical facility</td>
<td>2</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Failure to visit sub-investigator sites</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Late to start, big gaps, not to plan</td>
<td>11</td>
<td>32</td>
<td>43</td>
</tr>
<tr>
<td>IMP related issues</td>
<td>0</td>
<td>17</td>
<td>17</td>
</tr>
</tbody>
</table>
If you don’t have a monitoring plan
...and even when you do it is not followed...

......and even when it is followed its feedback loop is not acted on......

.........and key areas are omitted from the plan...

• Correct planning, design, priority setting and risk management would enable sponsors to:
  • ensure staff focus on what matters,
  • be more effective,
  • deliver good data,
  • convince regulator that process is in control
  • and that the choice of priorities is correct
  • and risk mitigation appropriate.
Analysis of inspection findings on monitoring and of other key areas.

- What are the issues for sponsors to improve?
- What are the issues for regulators to improve?
- Do they already have the correct emphasis?

- What were the major regulatory impacts – relationship between GCP non-compliance and marketing authorisation outcome?

- Scientific advice is linked to better outcome at MA – do sponsors who seek SA also fare better on inspection?
Thoughts for the day and for the future
Heisenberg uncertainty principle

- **uncertainty principle** - mathematical inequalities asserting a fundamental limit to the precision with which certain pairs of physical properties of a particle can be known simultaneously (e.g. position and momentum).

- **observer effect** the impact the act of observation has on a phenomenon being observed.
  - Querying, monitoring, auditing - by sponsors
  - Reviewing, questioning, inspecting – by regulators
  - All change behavior – people change the way they work, organizations change emphasis and process based on these.
  - All these are usually addressed with emphasis on negative rather than positive aspects
  - Beware of unintended consequences
Quality in clinical trials

Prioritization and risk mitigation approaches across several dimensions:

- Protection of trials subjects Rights, Safety, Integrity,
- Credibility of data and results

Stratified according to knowledge of product (MA status):

- Medicine authorised in EU used within terms of MA or within established treatment regimen
- Medicine authorised in EU used significantly outside of MA, Medicine without MA in EU

Customized approach depending on:

- Protocol complexity, extent of interventions related to trial
- Therapeutic indication and nature of endpoints, including population and co-medications
- Administration of the product, dose, formulation
- Complexity of study procedures and measurement, including the nature of the intervention
- Vulnerability of the study population
Clinical trial – product lifecycle

Phase I
Phase II
Phase III
Phase IV

Uncertainty
Protocol complexity
Knowledge of product

Weight of individual subject data
No. of subjects/patients treated

On site monitoring
Central monitoring

NB: The shape of the curves, crossover, etc. are not based on specific data. This is purely illustrative for discussion. Actual situation will vary case by case.
Resource

Resource is finite:

- Money
- Time – time in the day to get things done short term and elapsed time over long term

If you are designing a trial and have €1,000,000 to spend on it:

.... for each € 50,000 you decide to spend on one thing ....... you have € 50,000 less to spend on something else

..........so each time you decide you cannot live without a particular set of data/monitoring process/electronic gadget...decide what it is you are living without ....because it wont get done.

Instead of just taking a risk, prioritise and manage
Prioritise
Design

**Anticipate**
Assess risks, accept or mitigate
Revise design

Implement
Train, Do, Check, Review, Adjust
Train, Do, Check, Review, Adjust

Don’t just think of Corrective Action – implement with **Preventive** Action
“Perfection is achieved, not when there is nothing more to add, but when there is nothing left to take away.” — Antoine de Saint-Exupéry,
Thank you – questions – suggestions

GCP@ema.europa.eu