Protocol Deviations on Study Design, Statistical Evaluation and Efficiency in Drug Development: Some Improvements

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Outline

- Protocol Deviations
- Study Designs and Statistical Evaluation
- Conceptual Framework for Data Deviation
- Bias and Type I error
- Efficiency
- Concluding Remarks

*Research views presented are those of the authors and not necessarily of U.S. FDA*
ICH E-3: Protocol Deviations

All important *deviations* related to the *following 3 aspects* should be described, and, in the body of the text, should be appropriately summarized

- **Study inclusion or exclusion criteria**
  Entered the study even though did not satisfy the entry criteria

- **Conduct of the trial**
  Developed withdrawal criteria during study but weren’t withdrawn

- **Patient management or patient assessment**
  - Received the wrong treatment or incorrect dose
  - Received an excluded concomitant treatment

⇒ All 3 aspects also critical for adaptive design consideration

ICH E-3, Section 10.2
Quality assurance (QA) / quality control are an integral part of multicenter clinical trials involving radiotherapy*

Classification of Quality Assurance in radiotherapy
- Per-Protocol (PP)
- Deviation Acceptable (DA)
- Violation unacceptable (VU)
- Incomplete/Not Evaluable (I/NE)

* Radiation Oncology, 2009
ICH E-9: Protocol Deviations

- Identify important protocol deviations
- Common standards should be adopted for a number of features of the trials, e.g., handling of protocol deviations
- A careful explanation should be provided for deviations from the planned analysis
- Deviations from the planned procedure always bear the potential of invalidating the trial results
- If it is necessary to make changes to the trial, any subsequent changes to the statistical procedures should be specified in an amendment to the protocol at the earliest opportunity, especially discussing the impact on any analysis and inferences that such change may cause. The procedures selected should always ensure that the overall probability of type I error is controlled
ICH E-9: Protocol Violations

- May include errors in treatment assignment, the use of excluded medication, poor compliance, loss to follow-up and missing data

- The problems that lead to the exclusion of subjects to create the per protocol set, and other protocol violations, should be fully identified and summarized

- No clear distinction between deviation and violation in E-9

- Description of protocol violations in E-9 overlaps with the description of protocol deviations in E-3
1. Study inclusion or exclusion

Deviation: Those who entered the study even though they did not satisfy the entry criteria (ICH E3)

- **Inclusion criteria not pre-specified**
  - Unplanned patient expansion due to slow accrual
  - Unplanned enrichment due to low observe event rates
  - Criteria for entry clearly stated, but, unplanned sample size increase due to lower than anticipated clinical evaluable or pathological evaluable patient entry

- **Exclusion of patients from analysis not pre-specified**
  - Unplanned patient exclusion due to drug or SOC supply issue
  - No plan to exclude patients while still in the study, but, not all patients who entered the study & died were included in the mortality analysis
  - Reason for exclusion only formulated close or at the time of analysis, e.g., patients later determined to be ineligible or non-analyzable
2. Conduct of the Trial

Deviation: Those who developed withdrawal criteria during the study but were not withdrawn (ICH E3)

- Fixed design
  - No change in patient population, dose regimen, primary efficacy endpoints, but submit **protocol amendment to add/delete sites/regions**

- Open label versus blinded (or masked)
  - Trial implementation deviates from the protocol, difficult to maintain integrity on
    - Trial conduct
    - Trial logistics
    - Trial operation
  - May consider sub-structure of DMC if group sequential design
  - Encourage double-blinded study whenever possible
Deviation: those who received the wrong treatment or incorrect dose; those who received an excluded concomitant treatment

- Endpoint definition is critical to patient assessment
  - Sudden death in cardiac trial: Death within 60 minutes of the sudden onset of symptoms, whether or not death was related to re-hospitalization (unless an autopsy revealed a MI)
  - Intermediate biomarker is primary endpoint in oncology trial
    - reasonably likely to predict clinical endpoint not established yet
    - use early endpoint to predict intermediate biomarker
  - Objective measure of clinical cure in anti-infective trial
    - improvement in all clinically relevant signs and symptoms associated with primary cSSSI such that primary infection has been effectively treated and no further antibiotics are needed?
    - Objective def. : provide size criteria for the extent of infection
<table>
<thead>
<tr>
<th><strong>RESULTS</strong></th>
<th>13</th>
<th><strong>Flow of participants through each stage</strong> (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. <strong>Describe protocol deviations from study as planned, together with reasons.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recruitment</strong></td>
<td>14</td>
<td><strong>Dates defining the periods of recruitment and follow-up.</strong></td>
</tr>
<tr>
<td><strong>Baseline data</strong></td>
<td>15</td>
<td><strong>Baseline demographic and clinical characteristics of each group.</strong></td>
</tr>
<tr>
<td>Numbers analyzed</td>
<td>16</td>
<td><strong>Number of participants (denominator) in each group included in each analysis and whether the analysis was by &quot;intention-to-treat&quot;. State the results in absolute numbers when feasible (e.g., 10/20, not 50%).</strong></td>
</tr>
<tr>
<td><strong>Outcomes and estimation</strong></td>
<td>17</td>
<td><strong>For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval).</strong></td>
</tr>
<tr>
<td><strong>DISCUSSION</strong></td>
<td></td>
<td><strong>Interpretation of the results</strong>, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.</td>
</tr>
<tr>
<td>Interpretation</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Generalizability</td>
<td>21</td>
<td><strong>Generalizability (external validity) of the trial findings.</strong></td>
</tr>
<tr>
<td>Overall evidence</td>
<td>22</td>
<td><strong>General interpretation of the results in the context of current evidence.</strong></td>
</tr>
</tbody>
</table>
Intent-to-Treat Principle

The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e., the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed and analyzed as members of that group irrespective of their compliance to the planned course of treatment.

→ Basis for effectiveness assessment

ICH E-9
Per Protocol Set

Valid cases, Efficacy Sample, Evaluable subjects sample

The set of data generated by the subset of subjects who complied with the protocol sufficiently to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol violations

⇒ basis for efficacy assessment
Conceptual Framework for Data Deviation (protocol violation)

♦ Missing data including withdrawal (discontinuation) or censoring can occur at study baseline, during the course of the trial

♦ Validity of baseline data or outcome data can call into question with protocol violations or protocol deviations
  ♦ Patient classification at entry – phenotypic or genomic
  ♦ Outcome event or response definition
  ♦ Conduct of trial

♦ Sensitivity analysis considers different imputation methods for the ‘unobserved values’
Assume 20% response rate for treated and for placebo
In the extreme case when missing only occurs in treated
Superiority Objective

Power Issue

Assume mean response of missing subjects is between 0.20 to 0.40

Power in Intent-to-Treat versus Efficacy Analysis

N=200, $\pi_E=0.40$, Full Compliance, No Exclusions

N=160, $\pi_E=0.40$ When 40% missing in the treated arm

ITT, N=200

Outcome Probability in Excluded Subset, $\pi_{ex}$
### Non-inferiority Objective

**Type I Error Issue**

When treatment difference become apparent toward the study end

<table>
<thead>
<tr>
<th>Types of missingness and protocol deviation</th>
<th>PP</th>
<th>ITT (LVCF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random drop-out</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% 10% Pattern 1</td>
<td>0.026</td>
<td>0.046</td>
</tr>
<tr>
<td>10% 20% Pattern 2</td>
<td>0.025</td>
<td>0.130</td>
</tr>
<tr>
<td>20% 10% Pattern 3</td>
<td>0.026</td>
<td>0.030</td>
</tr>
<tr>
<td>30% 30% Pattern 4</td>
<td>0.028</td>
<td>0.12</td>
</tr>
<tr>
<td>Baseline-dependent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; &gt; Pattern 1</td>
<td>0.028</td>
<td>0.051</td>
</tr>
<tr>
<td>&gt; &lt; Pattern 2</td>
<td>0.030</td>
<td>0.034</td>
</tr>
<tr>
<td>&lt; &gt; Pattern 3</td>
<td>0.027</td>
<td>0.075</td>
</tr>
<tr>
<td>Due to lack of efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17% 17% Pattern 1 visit 2+</td>
<td>0.018</td>
<td>0.096</td>
</tr>
<tr>
<td>14% 12% Pattern 2 visit 3+</td>
<td>0.022</td>
<td>0.052</td>
</tr>
<tr>
<td>11% 8% Pattern 3 visit 4+</td>
<td>0.043</td>
<td>0.037</td>
</tr>
<tr>
<td>Non-compliance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% 10% Pattern 1</td>
<td>0.027</td>
<td>0.031</td>
</tr>
<tr>
<td>30% 30% Pattern 2</td>
<td>0.027</td>
<td>0.043</td>
</tr>
<tr>
<td>10% 30% Pattern 3</td>
<td>0.022</td>
<td>0.065</td>
</tr>
<tr>
<td>30% 10% Pattern 4</td>
<td>0.023</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Sanchez & Chen, SIM, 2006

Non-inferiority Objective

Type I Error Issue

When treatment difference become apparent early in the study

<table>
<thead>
<tr>
<th>Types of missingness and protocol deviation</th>
<th>T</th>
<th>C</th>
<th>PP</th>
<th>ITT (LVCF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random drop-out</td>
<td>10% 10%</td>
<td>Pattern 1</td>
<td>0.028</td>
<td>0.026</td>
</tr>
<tr>
<td>% dropouts</td>
<td>10% 20%</td>
<td>Pattern 2</td>
<td>0.026</td>
<td>0.057</td>
</tr>
<tr>
<td></td>
<td>20% 10%</td>
<td>Pattern 3</td>
<td>0.026</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>30% 30%</td>
<td>Pattern 4</td>
<td>0.030</td>
<td>0.029</td>
</tr>
<tr>
<td>Baseline-dependent</td>
<td>&gt;</td>
<td>&gt;</td>
<td>Pattern 1</td>
<td>0.027</td>
</tr>
<tr>
<td>20% of subgroup</td>
<td>&gt;</td>
<td>&lt;</td>
<td>Pattern 2</td>
<td>0.025</td>
</tr>
<tr>
<td>baseline &gt; 7.5</td>
<td>&lt;</td>
<td>&gt;</td>
<td>Pattern 3</td>
<td>0.024</td>
</tr>
<tr>
<td>Due to lack of efficacy</td>
<td>17% 17%</td>
<td>Pattern 1 visit 2+</td>
<td>0.074</td>
<td>0.002</td>
</tr>
<tr>
<td>if response &lt; 8.25 at visit+, discontinue</td>
<td>14% 12%</td>
<td>Pattern 2 visit 3+</td>
<td>0.080</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>11% 8%</td>
<td>Pattern 3 visit 4+</td>
<td>0.057</td>
<td>0.011</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>10% 10%</td>
<td>Pattern 1</td>
<td>0.026</td>
<td>0.031</td>
</tr>
<tr>
<td>loss of 20% efficacy due to noncompliance</td>
<td>30% 30%</td>
<td>Pattern 2</td>
<td>0.024</td>
<td>0.041</td>
</tr>
<tr>
<td></td>
<td>10% 30%</td>
<td>Pattern 3</td>
<td>0.024</td>
<td>0.065</td>
</tr>
<tr>
<td></td>
<td>30% 10%</td>
<td>Pattern 4</td>
<td>0.025</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Sanchez & Chen, SIM, 2006

## Bias Issue

### ITT vs. PP (when S vs. NI)

#### Efficacy Subset Bias

N = 100 per group

\[ \pi_C = \pi_E = 0.20 \]

<table>
<thead>
<tr>
<th>Percent Missing in Exp. Group</th>
<th>Control</th>
<th>Experimental</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \pi_C )</td>
<td>Max ( \pi_E^* )</td>
</tr>
<tr>
<td>0%</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>20%</td>
<td>0.20</td>
<td>20/80 = 0.25</td>
</tr>
<tr>
<td>40%</td>
<td>0.20</td>
<td>20/60 = 0.33</td>
</tr>
<tr>
<td>60%</td>
<td>0.20</td>
<td>20/40 = 0.5</td>
</tr>
</tbody>
</table>
Any patients excluded from the analysis deserve very close scrutiny particularly when the statistical significance of the results are reached by such exclusions
Any covariates added to the primary analysis model for adjustment deserve very close scrutiny particularly when the statistical significance of the results are reached by such inclusions
Need for Adopting Good Standards

- Failure to adhere to patient inclusion / exclusion criteria result in bias in results interpretation - mixture of ITT patient and those unintended
- Failure to adhere to treatment protocol deteriorates the study outcome in RCTs
- When important aspects of the study were later acquired - under designed
- Defective or poor definition (not carefully thought through) resulted in heterogeneous group
- Pre-plan ‘what to do’ when protocol deviations occur
First Principle of Adaptive Design

Prospectively planned modification of one or more specified aspect(s) of study design
Turn protocol deviations into efficient design and analysis

- Anticipate protocol deviation / protocol violation at planning
- Account for the types and the percentages
- Strategies to deal with incomplete data/data deviations
- Clinical scenario planning / Simulation studies
- Modeling - especially when the deviations or violations favor one group than another group
- Build in prospectively, inclusion/exclusion criteria allowing for acceptable deviations
- Prepare for change in trial conduct by establishing SOP and consider including independent 3rd party Charter
- Patient management and patient assessment: clear definition of clinical endpoint and clear description of key outcome measures for investigation