Introduction to Clinical Trials - Day 2

Session 4 - Trial Monitoring for Quality Control

Presented July 26, 2016

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Study Monitoring and Quality Control

Essential principle of good trial conduct

- Good trial conduct should include:

1. Masking (blinding)
2. Treatment allocation (randomization)
3. Study quality control
   - Data management
   - Data quality monitoring
4. Trial monitoring
   - Data quality
   - Safety
   - Interim decision and group sequential designs

Study Monitoring for Quality Control
Recruitment, retention, and compliance
Quality monitoring
Missing data
NRC Recommendations
Ex: CHEST trial

Essential principle of good trial conduct

Study quality control

- Key elements of study quality control include:
  1. Recruitment and retention
  2. Ongoing (monitoring) trial quality
     - Quality control of data and study processes
     - Site monitoring
     - Anticipating the unanticipated...
  3. Prevention and treatment of missing data

Study quality control

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Recruitment, retention, and compliance

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- Recruitment and retention:
  - Motivation
    - Most studies are only of scientific interest/relevance for a few years.
    - There is an ethical responsibility to participants to complete a trial once it is started.
    - One of the major reasons for closing studies is lack of accrual.
    - (One of the major reasons for suspending clinical research in an entire institution (closing the IRB) is old studies that are unlikely to be completed.)

"The most important part of good retention is good recruitment." (Richard Hamman, U Colorado)

Study quality control

Recruitment, retention, and compliance

- Recruitment and retention strategies:
  - Study design:
    - Choose intervention groups to encourage participation regardless of intervention group assignment.
    - Minimize trial burden
  - Sources for subjects:
    - Clinical practice
    - Previous trials
    - Patient registries
    - Health fairs (free screening, etc.)
    - Advertisements
  - Inducements:
    - Pens, coffee mugs,...
    - Reimbursement for time and inconvenience.
    - Payments beyond reimbursement are often considered unethical.

Study quality control

Recruitment, retention, and compliance

- Recruitment and retention strategies (Example: SLV HFP)
  - Study design:
    - Even ‘usual care’ group gets screening and education
    - Fasting blood measurements restricted to 12-month (i.e, not at 6 and 18 months)
  - Sources:
    - Medical practice records (groups and individuals)
    - Churches, parks and recreation.
    - Media
    - Health fair (diabetes screening)
    - Previous or ongoing diabetes studies
  - Inducements:
    - Some discussion of pens, coffee mugs,...

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Study quality control

Recruitment, retention, and compliance

- Recruitment and retention: monitoring and problem solving
  - Monitoring:
    - Annual IRB reports must summarize accrual
    - Investigators might track accrual of particular types of subjects (especially if sub-group analyses are important).
  - Problem Solving:
    - *Accept a smaller number of subjects
    - More rigorous recruitment
    - Extend the number of centers
    - Extend study time
    - *Relax eligibility or exclusions
    - *Recycle previous subjects

    *Can have serious (adverse) effects on study interpretation or generalizability.

Study quality control

Recruitment, retention, and compliance

- However, the best strategy for recruitment and retention that I have seen is to have:
  - A dedicated study nurse on site
  - Far better recruitment/retention if this person is familiar with the patients (culturally and personally)
  - Far better recruitment/retention if financial reimbursements for the site are (at least partially) paid up front

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Study quality control

Recruitment, retention, and compliance

- Compliance
  - Bias is decreased and power is increased when subjects complete the study and are fully compliant.
- It is important to design a study to maximize compliance:
  - Treatments should be defined/chosen to minimize the number of patients deemed non-compliant:
    - Define treatment as a single dose rather than multiple doses.
    - Incorporate ancillary treatments for adverse effects.
    - Modify treatments in presence of adverse effects.
  - Select compliant subjects:
    - Consider perception of potential benefit
    - Education level
    - Co-existing conditions (e.g., chronic conditions, drug abuse)
    - Questionnaires about patient beliefs, family support, etc.
    - Identify compliers with a run-in periods

Study quality control

Recruitment, retention, and compliance

- Methods for promoting compliance
  - Educating subjects:
    - Subjects who are informed of study goals will be better compliers.
    - Communication of potential problems before it is too late.
    - Establish difference between stopping treatment and quitting the study. (True for investigators as well!)
  - Minimize the trial burden:
    - Number and length of clinic visits.
    - Number of forms to be completed.
    - Number of painful procedures.

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Recruitment, retention, and compliance

- Disadvantages to promoting compliance:
  - May lengthen trial.
  - Subjects may notice change in therapy (run-in period).
  - Loss of generalizability (efficacy vs. effectiveness).
  - Compliant subjects may have lower event rates and thus potentially lower power (Good thing?).

Study quality control

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Demonstration of problems caused by poor compliance

- Compliance (adherence): The extent to which the subjects in a trial follow the treatment that was prescribed for them by the study protocol.
- Problem:
  - Subjects who do not comply with the treatment protocol will decrease statistical power of the study.
  - Non-compliance results in misclassification of some patients in each treatment group:
    - Drop-out: Non-compliant subjects on the new treatment arm.
    - Drop-in: Control subjects who take the new treatment.

Study quality control

Demonstration of problems caused by poor compliance

- Example: Clinical trial of fiber in prevention of colorectal polyps:
  - Endpoint: recurrent polyps within 3 years.
  - Hypotheses:
    - Low fiber: 45% recurrence
    - High fiber: 36% recurrence (20% reduction)
  - Sample size calculation:
    - (One-sided level $\alpha = 0.025$ test with power $\beta = 0.9$)

$$\begin{aligned} N &= \frac{(z_{0.975} + z_{0.90})^2}{(p_0 - p_1)^2}(p_0 q_0 + p_1 q_1) \\ &= \frac{(1.96 + 1.28)^2}{(0.45 - 0.36)^2}(0.45 \times 0.55 + 0.36 \times 0.64) \\ &= 620/arm \end{aligned}$$

Study quality control

Demonstration of problems caused by poor compliance

- Example (con't): Effect of drop-out
  - Suppose there is 75% compliance on the high fiber arm.
  - Attenuated treatment effect:
    - 75% have 36% recurrence
    - 25% have 45% recurrence
    - Overall $\approx$ 38% recurrence
  - Revised sample size:

$$\begin{aligned} N &= \frac{(z_{0.975} + z_{0.90})^2}{(p_0 - p_1)^2}(p_0 q_0 + p_1 q_1) \\ &= \frac{(1.96 + 1.28)^2}{(0.45 - 0.38)^2}(0.45 \times 0.55 + 0.38 \times 0.62) \\ &= 1035/arm \end{aligned}$$

Study quality control

Demonstration of problems caused by poor compliance

- Example (con't): Effect of drop-in
  - Suppose 10% of controls increase their fiber.
  - Attenuated treatment effect:
    - 10% have 36% recurrence
    - 90% have 45% recurrence
    - Overall $\approx$ 44% recurrence
  - Revised sample size:

$$\begin{aligned} N &= \frac{(z_{0.975} + z_{0.90})^2}{(p_0 - p_1)^2}(p_0 q_0 + p_1 q_1) \\ &= \frac{(1.96 + 1.28)^2}{(0.44 - 0.38)^2}(0.44 \times 0.56 + 0.38 \times 0.62) \\ &= 1406/arm \end{aligned}$$

Study quality control

Demonstration of problems caused by poor compliance

- Very naive solution: Treat non-compliant patients on the treatment arm as if they were on control.
  - Problem: Many studies have shown that non-compliant patients have lower survival than compliant patients (even on placebo).
  - Clearly this approach will tend to make any treatment look good.

Study quality control

Demonstration of problems caused by poor compliance

- Naive solution: Restrict analysis to compliant patients (“as treated analysis").
  - If non-comlpliant patients can be indentified and safely discarded from the analysis, then we would only need to inflate the sample sizes for each arm according to the rate of non-compliance.
- Example:
  - High fiber arm (25% drop-out)
    Accure 620/0.75 = 827
  - High fiber arm (10% drop-in)
    Accure 620/0.10 = 689
  - Compare the total of 1516 as opposed to $2 \times 1406 = 2812$ if the misclassified subjects are used.

Study quality control

Demonstration of problems caused by poor compliance

- Problems with naive solution:
  - Treatment may affect compliance:
    - Compliance is then an outcome of the treatment.
    - Can make bad treatments look good.
  - Non-compliers are different from compliers.
    - We can never know if the outcome in non-compliers would have been different if they had been compliant.
    - To leave them out of an analysis can create selection bias.

Study quality control

Failure of the As Treated Analysis

1. Drop-out is due to symptoms related to worsening of the disease; the treatment 'cures' the symptoms, but not the disease:
   - Control group will have more drop-outs, and those drop-outs will be the ones with bad disease.
   - As treated analysis will make the treatment look bad because the worst control patients are ignored.

Study quality control

Failure of the As Treated Analysis

2. Drop-out due to perception of getting the worse treatment:
   - Patients have a bias toward the new treatment.
   - Worsening condition on placebo leads to non-compliance.
   - Worsening condition on new treatment has no effect on compliance.
   - As-treated analysis makes new treatment look bad.
   - (Example: early AIDS trials.)

Study quality control

Failure of the As Treated Analysis

3. Drop-out due to adverse events, but concordance between adverse events and treatment outcome differs between treatment arms:
   - Adverse events might indicate better prognosis on the treatment arm and worse prognosis on the control arm
   - Example: Chemotherapy in cancer
     - Nausea and vomiting can be caused both by progressive disease and by the treatment.
     - Treatment arm: greater side effects tend to go with higher anti-tumor effects.
     - Control arm: greater side effects tend to go with disease progression.
     - As treated analysis can make treatment look bad.

Study quality control

Failure of the As Treated Analysis

4. Drop-out due to treatment harm:
   - Example: Chemotherapy in cancer
     - New chemotherapy cannot be tolerated by the patients with poor prognosis (or even worse, treatment causes adverse outcomes that lead to non-compliance).
     - Control arm has no tolerance problems and good compliance.
     - As treated analysis makes the treatment look good by ignoring its failures.

Study quality control

Demonstration of problems caused by poor compliance

- Solution:
  - Primary efficacy analysis should generally be based on intention-to-treat
    - Analyze patients according to the treatment they were randomized to
  - (discussed as part of Statistical Analysis Plan)
- See also: National Academies Panel on Prevention and Treatment of Missing Data (discussed below)

Study quality control

Monitoring study quality

- Although the trail must be designed to assure quality, that quality must be monitored as part of trial conduct.
  - Data QC
  - Monitoring accrual, compliance, and retention as discussed above
  - Problems must be discovered and corrected ASAP
  - Example of what I monitor for data quality
    - Data consistency monitoring (software checks)
    - Regular reports on missing data, protocol deviations, etc.
    - Reports on eligibility and exclusion criteria (and exceptions)
    - Randomization integrity (randomized subjects must receive treatment)
    - Adherence to visit schedules

Study quality control

Monitoring study quality

- Site monitoring:
  - Most multi-center trials send site monitors to all sites to confirm:
    - Treatments and procedures are following protocol.
    - Data in trial database matches information in patient charts.
    - Discrepancies are reported to sponsor and site PI must correct.

Prevention and treatment of missing data

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Missing data
NRC Recommendations
Ex: CHEST trial

How can there be missing data?

- Consider 3 mechanisms by which missing data in trials arise:
  - Non-compliance:
    - Subject stops the assigned treatment
    - Outcome measurements are obtained
    - Missing the outcome measure that would have been obtained if the subject had remained on treatment.
    - Solution: Intention-to-treat analysis
  - Withdrawal of consent:
    - Subject withdraws from the study (it is their right).
    - Outcome measurement cannot be obtained
    - Subjects should be offered the opportunity to remain on the study but stop all interventions and still return for outcome measurements (i.e., non-compliant).
  - Loss-to-followup:
    - Subjects have left the study and cannot be contacted.
    - Avoidable through good study management.
    - We should not accept loss-to-followup.

Prevention and treatment of missing data

Impact of missing data

- Missing data decrease trial quality:
  - Cannot rule out bias due to differences between those who are observed and those who are not.
  - Avoid missing data through careful definition of endpoints.
    - Identify the most important endpoints and make sure they are measured.
    - Use outcomes that are easy to obtain (mortality vs tumor progression).
    - Define the endpoint so that data which are impossible to observe are assigned a meaningful value:
      E.g., Quality of life after death = 0.
  - Statistical adjustments are always based on untestable assumptions:
    - MNAR: missing not at random. Missing data mechanism differs from the relationships that are observed in the non-missing data.

Prevention and treatment of missing data

How big of a problem is missing data in clinical trials?

- The National Academies recently convened an expert panel of statisticians to discuss the prevention and treatment of missing data, including
  - Standardizing terminology
  - Enforcing the idea that the best way to deal with missing data is to not have missing data
  - Provide recommendations to avoid missing data
  - Provide recommendations for addressing missing data in trial analyses

The Prevention and Treatment of Missing Data in Clinical Trials

ISBN
978-0-309-15814-5

162 pages
6 x 9
PAPERBACK (2010)

Panel on Handling Missing Data in Clinical Trials; National Research Council

Prevention and treatment of missing data

- Contents of NRC report:

1 Introduction and background
2 Trial designs to reduce the frequency of missing data
3 Trial strategies to reduce the frequency of missing data
4 Drawing inference from incomplete data
5 Principles and methods of sensitivity analyses
6 Conclusions and recommendations:
   - *Trial Objectives*: Recommendation 1
   - *Reducing dropouts through trial design:* Recommendations 2, 3, 4, 5.
   - *Reducing dropouts through trial conduct:* Recommendations 6, 7, 8.
   - *Treating missing data:* Recommendations 9, 10, 11, 12, 13, 14, 15.
   - *Understanding the causes and degree of dropouts in clinical trials:* Recommendations 16, 17, 18.

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Recommendations of the NRC report

Recommendation 1:

- The trial protocol should explicitly define the objective(s) of the trial; the associated primary outcome or outcomes; how, when, and on whom the outcome or outcomes will be measured; and the measures of intervention effects, that is, the causal estimands of primary interest.

- These measures should be meaningful for all study participants, and estimable with minimal assumptions. Concerning the latter, the protocol should address the potential impact and treatment of missing data.

Prevention and treatment of missing data

Recommendations of the NRC report

Recommendation 2:

- Investigators, sponsors, and regulators should design clinical trials consistent with the goal of maximizing the number of participants who are maintained on the protocol-specified intervention until the outcome data are collected.
- (see previous discussion)

Prevention and treatment of missing data

Recommendations of the NRC report

Recommendation 3:

- Trial sponsors should continue to collect information on key outcomes on participants who discontinue their protocol-specified intervention in the course of the study, except in those cases for which a compelling cost-benefit analysis argues otherwise, and this information should be recorded and used in the analysis.
- Treatment discontinuation does not equate to study discontinuation!

Prevention and treatment of missing data

Recommendations of the NRC report

Recommendation 4:

- The trial design team should consider whether participants who discontinue the protocol intervention should have access to and be encouraged to use specific alternative treatments.
- Such treatments should be specified in the study protocol.

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Recommendations of the NRC report

Recommendation 5:

- Data collection and information about all relevant treatments and key covariates should be recorded for all initial study participants, whether or not participants received the intervention specified in the protocol.

Prevention and treatment of missing data

Recommendations of the NRC report

Recommendation 6:

- Study sponsors should explicitly anticipate potential problems of missing data. In particular, the trial protocol should contain a section that addresses missing data issues, including the anticipated amount of missing data, and steps taken in trial design and trial conduct to monitor and limit the impact of missing data.

Prevention and treatment of missing data

Recommendations of the NRC report

Recommendation 7:

- Informed consent documents should emphasize the importance of collecting outcome data from individuals who choose to discontinue treatment during the study, and they should encourage participants to provide this information whether or not they complete the anticipated course of study treatment.

Prevention and treatment of missing data

Recommendations of the NRC report

Recommendation 8:

- All trial protocols should recognize the importance of minimizing the amount of missing data, and, in particular, they should set a minimum rate of completeness for the primary outcome(s), based on what has been achievable in similar past trials.

Prevention and treatment of missing data

Recommendations of the NRC report

Recommendation 9:

- Statistical methods for handling missing data should be specified by clinical trial sponsors in study protocols, and their associated assumptions stated in a way that can be understood by clinicians.

Prevention and treatment of missing data

Recommendations of the NRC report

Recommendation 10:

- Single imputation methods like last observation carried forward and baseline observation carried forward should not be used as the primary approach to the treatment of missing data unless the assumptions that underlie them are scientifically justified.

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Recommendations of the NRC report

Recommendation 11:

- Parametric models in general, and random effects models in particular, should be used with caution, with all their assumptions clearly spelled out and justified. Models relying on parametric assumptions should be accompanied by goodness-of-fit procedures.

Prevention and treatment of missing data

Recommendations of the NRC report

Recommendation 12:

- It is important that the primary analysis of the data from a clinical trial should account for the uncertainty attributable to missing data, so that under the stated missing data assumptions the associated significance tests have valid type I error rates and the confidence intervals have the nominal coverage properties.
- For inverse probability weighting and maximum likelihood methods, this analysis can be accomplished by appropriate computation of standard errors, using either asymptotic results or the bootstrap.
- For imputation, it is necessary to use appropriate rules for multiply imputing missing responses and combining results across imputed datasets because single imputation does not account for all sources of variability.

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Recommendations of the NRC report

Recommendation 13:

- Weighted generalized estimating equations methods should be more widely used in settings when missing at random can be well justified and a stable weight model can be determined, as a possibly useful alternative to parametric modeling.

Prevention and treatment of missing data

Recommendations of the NRC report

Recommendation 14:

- When substantial missing data are anticipated, auxiliary information should be collected that is believed to be associated with reasons for missing values and with the outcomes of interest.
- This could improve the primary analysis through use of a more appropriate missing at random model or help to carry out sensitivity analyses to assess the impact of missing data on estimates of treatment differences.
- In addition, investigators should seriously consider following up all or a random sample of trial dropouts, who have not withdrawn consent, to ask them to indicate why they dropped out of the study, and, if they are willing, to collect outcome measurements from them.

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Recommendations of the NRC report

Recommendation 15:

- Sensitivity analyses should be part of the primary reporting of findings from clinical trials.
- Examining sensitivity to the assumptions about the missing data mechanism should be a mandatory component of reporting.

Prevention and treatment of missing data

Recommendations of the NRC report

- The NRC Panel recommendations have made an impact on funding agencies, regulatory agencies, and journals
- Since they have emerged, FDA has consistently required multiple sensitivity analyses be pre-specified in the Statistical Analysis Plan

Prevention and treatment of missing data

Recommendations of the NRC report

- Commonly requested sensitivity analyses include some combination of:

1. Multiple imputation
2. Inverse probability weighted estimator
3. “Worst case" scenario
   - Assume best observed outcome in control and worst observed outcome in treatment
4. Pattern mixture models
   - Semi-parametric (shift) model on differences in missing values between treatment and control subjects
   - Generally range from worst case scenario to no difference
5. “Tipping point" analysis
   - How bad do imputed differences between treatment and control have to be in order to change results?

Prevention and treatment of missing data

Ex: CHEST trial

- Example: CHEST trial: Ghofrani,*et.al.* NEJM (2013); 369: 319-29: Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension.
  - Trial: Randomized double-blind placebo controlled trial in patients with inoperable CTEPH.
  - Primary endpoint: 16-week change in 6-minute walk distance (6MWD)
  - Summary of outcome: mean change denoted by θ_1 (riociguat) and θ_0 (placebo)
  - Measure of treatment effect: $\theta = \theta_1 - \theta_0$.
  - Results: "...By week 16, the 6-minute walk distance (had increased by a mean of 39 m in the riociguat group, as compared with a mean decrease of 6 m in the placebo group (least-squares mean difference, 46 m; 95% confidence interval [CI], 25 to 67; P<0.001)."

Prevention and treatment of missing data

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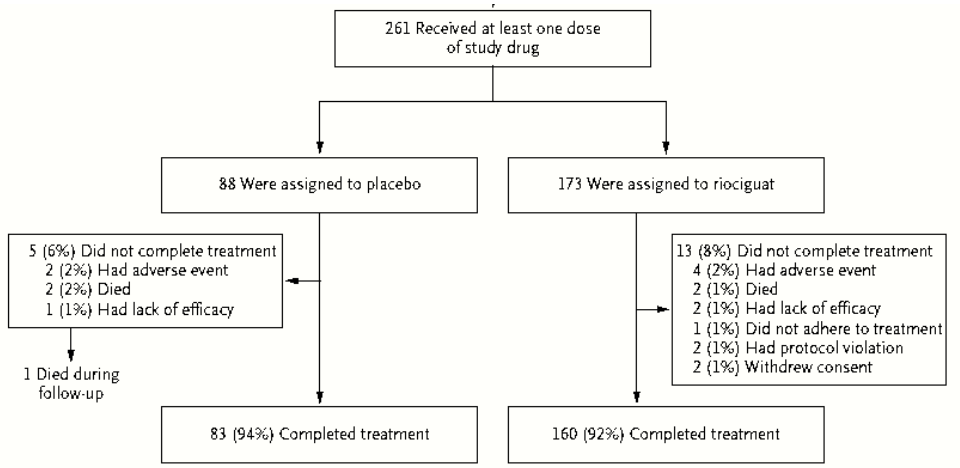
Ex: CHEST trial

- Missing data in CHEST trial:



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Prevention and treatment of missing data

Ex: CHEST trial

- Analysis based on modified intention-to-treat population, defined as all patients who underwent randomization and received at least one dose of the study medication
- Pre-specified imputation for missing data:
  - Patients who died or withdrew due to clinical worsening without terminal visit:
    - 6MWD at 16 weeks set to worst possible value: 0 meters
  - Patients who stopped study medication prematurely:
    - 6MWD at 16 weeks set to value at terminal visit or last visit post baseline.

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Ex: CHEST trial

- Pre-specified sensitivity analyses for missing data:

Table S1. Change in 6-Minute Walk Distance from Baseline: Sensitivity Analyses (Modified Intention-To-Treat population).

Analysis	Estimated Treatment Difference* (m)	95% Confidence Interval
Multivariate linear model at week 16	44.40	27.94 to 60.85
Multiple imputation: fixed penalty: riociguat –60 m and placebo –60 m	43.69	26.25 to 61.13
Multiple imputation: decreasing slope: riociguat –20 m and placebo –20 m per visit	41.81	24.05 to 59.58
Multiple imputation: fixed penalty: riociguat –60 m and placebo –0 m	40.07	22.94 to 57.21
Multiple imputation: decreasing slope: riociguat –20 m and placebo –0 m per visit	38.71	21.27 to 56.15

* Riociguat – placebo

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- Conclusion (from the paper):

  “At week 16, the 6-minute walk distance had increased from baseline by a mean of 39 m in the riociguat group, as compared with a mean decrease of 6 m in the placebo group (least-squares mean difference, 46 m; 95% confidence interval [CI], 25 to 67; P<0.001), on the basis of an analysis of the modified intention-to-treat population with missing values imputed (Table 2 and Fig. 2). In sensitivity analyses for missing data that used statistical methods for longitudinal data (see the Supplementary Appendix), the benefit of riociguat was similar to that observed in the main analysis (Table S1 in the Supplementary Appendix)."