Quality Assurance, Data Collection, Data review

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Data Collection

• General Organization of Data Collection Forms
• Visit Format
• Grouping by Integration (eg all PE forms)
• Combining visit and data
Designing the Data Collection Forms

• Standardized Information and Forms
• Patients initials, study number, date of visit
• Use jargon and terminology suitable to the study
• Precoded synonyms or codes may be used on the form
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<sup>a</sup> Dosing: iv infusion of placebo, 5 mg, 40 mg TRK-820 over 5 min; iv infusion amoxicillin 400 mg over 4 hours
<sup>b</sup> 24 and 48 hour post last dose follow up
<sup>c</sup> Blood pressure and heart rate measurements: 0 (immediately before dose), 5 min, 15 min, 60 min, 2 hr, 4 hr, 6 hr, 8 hr, 12 hr, 24 hr
<sup>d</sup> Laboratory sample collected at screening, on each dosing day immediately before dosing and at the end of the study (48 post last dose)
<sup>e</sup> Urinary collection for TRK-820 and human metabolites: collected at screening and end of study; on dosing days for the following periods: 2 to 0 hr (prior to dose), 0 to 2 hr, 2 to 4 hr, 4 to 6 hr, 6 to 8 hr, 8 to 12 hr, 12 to 24 hr
<sup>f</sup> 12-lead ECG read locally for safety
<sup>g</sup> If 12 recording device, read by core laboratory; time points: 0 (immediately before dose), at Tmax (-5 min), 15 min, 30 min, 60 min, 2 hr, 4 hr, 6 hr, 8 hr, 12 hr, 24 hr
<sup>h</sup> Sampling for TRK-820, human metabolites 0 (immediately before dose), 5 min, 15 min, 30 min, 60 min, 2 hr, 4 hr, 6 hr, 8 hr, 12 hr, 24 hr
<sup>i</sup> ECG and PK sample 48 hrs post last dose
Backward and Forward Approach

• Backward and forward approach
• Backward approach, start with idea of information, format in stat report or synopsis
• Then tracked back to the design of the form
• Allows easy conversion to data tables
Forward Approach

• Considers the type and quantity of raw data to be collected
• Designs data forms around these data
• Important to consider data integration from multiple sites
Backward of Forward

- Eventually by using either approach
- Appropriate Data forms are established
- Be sure the forms are usable from center to center
Types of Generic Data Collection Forms

- Patient demographic
- PMHX
- Chemistry, CBC, UA
- Radiology forms, Ekg forms
- Neurological exam
- Pk forms
- QOL tests
- Concomitant medications
- Medicine dose for acute and chronic trial
- Medicine dispensing record
- Compliance check pill count
- Adverse reaction summary
- Adverse reactions time, onset and cessation
- Clinical global impression by PI and by patient
- Efficacy measurements
- Termination record
- Post termination follow up
- Investigatory comment log
Specialized Data Collection Forms

- Often useful to give a checklist of procedures to be performed on a certain visit
- Time and events schedule is also helpful
Post treatment data

• Patient cannot be discharged from the study, because of adverse reaction, abnormal labs or other factors
• May require a separate form
• May be put into the investigators log
Measuring and recording parameters

- For eg if running a trial in which hematuria is important
- May wish to code and map various terms
- UA
- 0 is none
- 0.5 trace
- 1 slight, mild, 1 plus
- 2 moderate, 2 plus
- 3 marked, 3 plus
- 4 marked, 4 plus
Pitfalls to avoid in designing data collection forms or determining the amount of data to collect at various time points

- Requesting information, but not adequate instruction in how to complete the form
- Multiple pages or use of single page
- Try to eliminate jargon unfamiliar to persons filling out forms
- Check off system with no other category
- Collecting data as write in... data integration is hard
- Codes used for data processing used on forms can be hard for PI and study personnel
- Not combining forms in an easy manner for study personnel
Other pitfalls

- Determining the amount of data to collect at different time points in one or multiple trials
- Not collecting data at baseline or posttreatment
- Not collecting any data at relevant time points, EKG at baseline, but not for example if QT effect
- Not collecting data at adequate time points
- Collecting unnecessary data
Closed vs Open System

- Closed system 100% pre printed multiple choice responses
- Open system lines where responses can be written
- In multicenter trials units of measurement need to be standardized across the trial (check that the laboratories used in the trials are using the same standardized units)
- May want to use conversion factors
- Category of NA may be appropriate on some forms
Touchstones for determining the amount of data to be collected

• Are these data necessary to meet the requirements of the protocol

• How will data compare to date generated from other clinical trials if they need to be combined into a regulatory submission

• How will data be treated in reports
Completing the Data Collection Forms

• Sponsor trial, site PI and research colleagues should evaluate forms for completion
• In non sponsor, investigator should have a colleague assess completion of forms
• Folks who are entering data should also take a look at the forms
• Signing the data collection form
Eg of steps used to process data from a clinical trial

- Data retrieval
- Programming computers for data entry
- Integrating samples to outside laboratory
- Data entry
- Editing of data
- Querying data
- Correcting data
- Quality assurance and release of data
- Statistical analyses
- Draft statistical report
- Clinical interpretation
- Final statistical report
- Final medical report
Improving the efficiency of data flow

- Design standard operating procedures that are simple to use
- Design standard data collection forms
- Use data collection forms that are simple, check mark vs write in
- Explore automation eg optical scanning, remote data entry
Data Retrieval

- Strategy
- Collecting on an ongoing basis
- Using batch mode
- Waiting until the clinical trial is completed
Data Retrieval

• Data is retrieved by monitors
• Mail
• Next day courier service
• Fax
• Telephone transmission
Data Collection Goal

- Data base lock after last patient entered into the study

- Acceptable error rates after quality assurance and release of data is 1 to 10 errors/10000 fields
Audit Trail

• When errors are detected, during data review, record must be maintained
• May be assessed by FDA or European authority
• The later the changes are found, more work to reconcile the documents
Errors Detected

- Errors detected by monitors during editing require change to original, and investigators copy of the data entry form.
- Log also must be maintained
- Accuracy of most data collection forms is 75 to 85%
- Online data entry 95 to 99%
- Any errors in reporting of safety may require opening of data base
<table>
<thead>
<tr>
<th>Issue</th>
<th>Formal interim analyses</th>
<th>Informal interim analyses</th>
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<tr>
<td>Timing</td>
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<td>More frequent</td>
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<td>Development Stage</td>
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<td>IIab, IIIab</td>
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<tr>
<td>Protocol statement</td>
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<td>no</td>
</tr>
<tr>
<td>Purpose</td>
<td>Clinical trial is modified or terminated</td>
<td>Should new trial be initiated</td>
</tr>
<tr>
<td>Adjustment made to significance</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>
Types of Data that may be assessed

- Safety
- Efficacy
- QoI
- PK
- Pharmacoeconomic
Groups that may receive Interim Analyses

- Data Monitoring committee independent of sponsor
- Sponsor review committee
- Clinical monitors or staff
- Investigator conducting the trial
Selected Outcomes of interim analyses

- No effect on clinical trial
- Minor modification, that do not require IRB approval
- Major modification requiring IRB approval
- Modifications to other ongoing trials
- Termination of trial
- Modification to development strategy of medicine or therapy
Data Review Committee

• investigators may plan an interim analysis, preferably conducted by an independent data monitoring committee (IDMC).

• The task of the IDMC is to assess whether the ongoing trial realistically can be expected to answer its primary question, taking into account the following aspects:

•
• 1. Is the inclusion rate of patients acceptable and as expected?
• 2. Is there an unexpectedly high rate of severe or life-threatening adverse events, which may indicate the premature closure of the trial?
3. Is the outcome of the trial treatment comparable with that of the previous experience upon which the specific trial is based? The answer to this question is of particular importance in early phase III multicenter trials, which are based on results from smaller phase II trials performed at one or few institutions. It is well known that the results of such limited phase II studies are often superior to the outcome of multicenter studies because of different patient selection.
4. Do the results of the interim analysis prove statistically significant differences between the trial treatments that exceed the differences defined by the statistical guidelines of the trial? This would warrant closure of the study. This policy led, for example, to premature closure of two large trials testing the role of metoprolol in chronic heart disease\(^1\) or simvastatin in hypercholesterolemia.\(^2\) Clearly defined prior to the start of a trial

- a. Should the trial be stopped if test treatment is significantly better than placebo
- b. Should trial be stopped if no statistical difference between placebo
- c. Should trial be stopped if test treatment is worse than placebo
Qualifications

- Expertise
- Experience in randomized and controlled trials
- Integrity
- Common sense
- Knowledge of statistical principles
Issues

• Blind vs open statistical analyses of data
• Scope of data to be given to the committee, baseline data, safety data, efficacy data, quality assurance data, projections of recruitment, times to study milestones
Issues to consider if unblinding

- Special issues or problems is committee is blinded
- Consideration of data from other sources
Committee Output

• Statement to the trials organizers
• Ad hoc report to federal authorities
• Reports regarding relevant data, clinical trial conduct, or regarding trial continuation
• Report to the ethics committee
• Any other appropriate statement
Stopping rules

• May be based on efficacy
• Statistically set boundaries
Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR Study)
CHOIR Hypothesis

• Compared outcomes of CKD patients randomly assigned to treatment groups that differed only in targeted hemoglobin levels
  • Hb 11.3 v. 13.5 g/dL
• Tested primary hypothesis that the level of anemia correction with once weekly dosing of epoietin-alfa in patients with chronic kidney disease decreases mortality and cardiovascular morbidity
Study Design

- Open label, Randomized Controlled Trial
- 130 sites randomized subjects in the United States
- 3 years duration
  - First patient randomized on April 17, 2002, last patient randomized on May 25, 2004
  - The last patient terminated on August 23, 2005
- 2,000 patients initially planned (randomized 1432 subjects)
- Study population
  - Hb < 11 g/dl
  - Age ≥ 18
  - Steady-state GFR ≥ 15 ml/min and ≤ 50 ml/min
Key Exclusion Criteria

- Uncontrolled hypertension
- Iron overload (TSAT) >70% or ferritin >1000 ng/mL
- Unstable angina pectoris or angina at rest
- Refractory iron deficiency anemia (TSAT is < 20% despite appropriate IV iron repletion)
- Currently receiving rHuEPO or having received it within 3 months of study entry.
Endpoints

Primary Endpoint: Composite event consist of

- Death
- Myocardial infarction
- Stroke
- CHF hospitalization (excluding RRT)
Myocardial infarction
2 of the following
• Chest pain for \( \geq 15 \) minutes
• Abnormal cardiac enzymes
• New EKG findings suggestive of MI

Stroke
• A new neurologic deficit of sudden onset that is not reversible within 24 hours and which is not due to a readily identifiable non vascular cause (i.e brain tumor, trauma)

CHF Hospitalization
• Unplanned CHF presentation requiring admission during which patient received IV therapy with inotropes, diuretics or vasodilators. (Hospitalization involving renal replacement therapy excluded)
Clinical Endpoints Committee

- Events were triggered off the case report form
- Sites were queried for source documents
- Source documents were reviewed by committee to see if a priori definitions of the outcomes were met
- Entered into the clinical data-base as an event
Secondary Endpoints

- All cause mortality
- CHF hospitalization
- Myocardial infarction
- Stroke
- Renal replacement therapy
- Cardiovascular hospitalizations
- All cause hospitalizations
Secondary Endpoints

• Change from baseline in hemoglobin/hematocrit, epoietin dose, iron stores

• Development of incident CHF (determined using NHANES I criteria)

• Change from baseline in Glomerular filtration rate,

• Health related quality of life and functional status
Study Treatments

GROUP A: Epoietin-alfa therapy directed at maintaining the hemoglobin level as close to 13.5 g/dL as possible

GROUP B: Epoietin-alfa therapy directed at maintaining the hemoglobin level as close to 11.3 g/dL as possible

Initial Hb targets: 10.5-11 and 13-13.5 g/dL.  Changed 11/02
Epoeitin-alfa dosing and Hb Monitoring

• Epoeitin-alfa dosing:
  • Epoeitin-alfa 10,000 Units s.c. q week x 3 weeks
  • After three weeks at this level, Epoeitin-alfa were adjusted based on hb response using an algorithm provided to the sites.
  • Epoeitin-alfa dosed weekly initially. When hb reached target and epoeitin-alfa was not adjusted for one month, the dose was doubled and delivered once every two weeks.

• Hb Monitoring:
  – Initially every other week
  – When Hb reached target and stabilized, monitoring changed to monthly.
**CHOIR**

**PROCRIT Dosing Algorithms for Patients on Weekly Dosing**

### Group A: Target Hgb 13.5

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<th>Range</th>
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<th>11.6 to 12.0</th>
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<td>+5000</td>
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### Group B: Target Hgb 11.3

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<tr>
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<td>NC</td>
<td>-2000</td>
<td>-2000</td>
<td>-4000</td>
<td>Hold</td>
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*All specified dose changes are in relation to the last dose the patient actually received.*

*The algorithm is designed to provide dose adjustments for subjects who are continuously managed based on the algorithm and who fall into typical patterns of response. Dosing will need to be individualized for subject who for one reason or another are not continuously managed based on the algorithm or whose clinical course may be atypical (e.g., individuals who require very low doses of Procrit or individuals whose doses are held for extended periods of time). Maximum dosage is 20,000 units if a specified dose reduction would result in a new dose of 0 or less, then the decrease in dose should be limited to 50% of the patient's current dose.*

*Transfusions: In the event that a patient receives a RBC transfusion during the study period, no change (NC) will be made to the dose until 2 consecutive Hb values have been obtained post-transfusion.*
Interim Analyses and Study Early Termination

- Four interim analyses to be evaluated by DSMB were planned with early stopping guidelines for efficacy and futility evaluation.
- Second interim analysis in May 2005 based on 145 events showed a trend of higher event rate in high Hb arm than low Hb arm.
- The estimated conditional power was less than 5% to demonstrate the reduction of composite event rate for the high Hb arm over low Hb arm as originally planned.
- DSMB recommended to stop the study in May 2005 after all possible considerations – Sponsor concurred.
Statistical Methods

• The primary efficacy analyses were conducted on all randomized patients based on the intention to treat principle.

• The primary endpoint of composite events and individual event types were estimated using Kaplan-Meier method and compared between the two treatment groups using the log-rank test.

• Cox proportional hazard model was used to estimate the hazard ratio.
CHOIR: Patient Flow

1432 patients, 130 centers, US only
Epoetin-alfa

Randomization

Median f/u 16 months

High target Hb (13.5 g/dl) n=715

Low target Hb (11.3 g/dl) n=717

Statistical Power 80% to detect a 25% reduction in composite event rate in high Hb group over 3 years

Enrollment and Outcomes

Baseline characteristics similar except for:

Higher rate of self-reported history of hypertension in high Hb arm (P=0.03)

Higher rate prior coronary-artery bypass grafting in the high-hemoglobin group (P=0.05).
Mean Monthly Hemoglobin Levels (Panel A) and Mean Weekly Doses of Epoetin Alfa (Panel B)
Kaplan-Meier Plot of the Time to the Primary Composite Event between Randomization and Termination: ITT Population

Primary Composite Endpoint:
Death, MI, CHF hosp (no RRT) and/or stroke

Hazard ratio 1.337 (1.025, 1.743)
P = 0.0312
Components of the Primary Endpoint

- Death:
  - Hazard ratio: 1.483 (0.969, 2.268)
  - p = 0.0674

- CHF Hospitalization (where RRT did not occur):
  - Hazard ratio: 1.389 (0.967, 2.054)
  - p = 0.0727

- Stroke:
  - Hazard ratio: 1.010 (0.454, 2.249)
  - p = 0.9803

- Myocardial Infarction:
  - Hazard ratio: 0.915 (0.484, 1.729)
  - p = 0.7836
Summary of Results

Primary Composite Event

Death

CHF Hospitalization

Myocardial Infarction

Stroke

13.5g/dL target better

11.3g/dL target better
RRT outcome time to (RRT)

Hazard ratio 1.186 (0.941, 1.495)
P= 0.1467
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<tr>
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<th>Low</th>
<th>Difference</th>
<th>P-value</th>
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<td>97</td>
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<td>0.0312</td>
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<tr>
<td>Observed Event Rate</td>
<td>17.5%</td>
<td>13.5%</td>
<td>4.0%</td>
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<tr>
<td>K-M Estimated Event Rate by the End of 3rd Year</td>
<td>29.5%</td>
<td>24.9%</td>
<td>4.6%</td>
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<tr>
<td>Hazard Ratio (95% CI)</td>
<td>1.377 (1.025, 1.743)</td>
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</table>
Quality of Life

- The patients' quality of life (as assessed by LASA, KDQ, and SF-36 scores) showed similar levels of improvement from baseline values in both groups, except for the score for the emotional role subscale of the SF-36, which was significantly higher in the low-hemoglobin group.
Summary

• Targeting Hb to 13.5 g/dL associated with an increased risk of composite event of death, MI, CHF hospitalization, and stroke
  – Observed event rate was 17.5% (High Hb arm) vs. 13.5% (Low Hb arm)
  – KM estimated event rate by the end of the 3rd year was 29.5% (High Hb arm) vs. 24.9% (Low Hb arm), p = 0.03
  – HR of 1.337, CI 1.025, 1.743
The primary endpoint was driven by a higher incidence of death and CHF hospitalization

• Further Analyses are being conducted, including identifying other risk factors associated with the composite events.
Conclusions

• Targeting of Hb to 13.5 g/dL has increased risk in CKD patients compared to a Hb target of 11.3 g/dL
• Our strong recommendation is to target and maintain Hb in range of 11-12 g/dL in all CKD patients
• We would not recommend following the current NKF K-DOQI Anemia Update recommendation 2.1.2
# Causes of Death

<table>
<thead>
<tr>
<th>Causes</th>
<th>Hb 13.5</th>
<th>Hb 11.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Related</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Thrombotic</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>ESRD</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Deaths</td>
<td>52 (7.31%)</td>
<td>36 (5.07%)</td>
</tr>
</tbody>
</table>