FDA REGISTRATION TRIALS: A DATA MANAGEMENT PERSPECTIVE

Louise Highleyman, S1400
Diana Heaney, S1404
SWOG Data Operations Center
Overview

- Registration Trials
- Practical Implications
- Data Coordinator Review
- Centralized Monitoring
- Resources
- Examples from S1404 and S1400
What is a registration trial?

- A trial that is branded "registration" means that it is planned to move forward for review by the FDA as either a new agent, or to expand the labeling for new indications.

- Currently enrolling SWOG registration trials:
  - S1400 & sub-studies S1400G, S1400I (Lung-MAP)
  - S1404 (Melanoma)
  - S1418 (Breast)
  - S1605 (GU)
Practical Implications

• In general, data procedures are the same
• Increased data submission requirements
  ◦ More detailed adverse event reporting
  ◦ Concomitant medication forms
  ◦ Increased reporting of laboratory values
• Radiology image submission (TRIAD)
• Increased attention to EDC and source documentation
  ◦ Data coordinators, centralized monitoring, auditing
Practical Implications

- Protocol-specific training requirements
  - Slide shows or instructional videos
- SWOG audits are done more frequently
- Data reporting requirements might be adjusted to gather additional information for further analysis, or in reaction to a changing medical landscape
- Increased potential for an FDA audit
Data Coordinator Review

- Higher frequency of review; more data fields to review
- Common queries from Data Coordinators:

<table>
<thead>
<tr>
<th>S1404</th>
<th>S1400 Sub-Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>T and N staging (Onstudy)</td>
<td>TNM staging (Onstudy)</td>
</tr>
<tr>
<td>Total no. of nodes removed (Onstudy)</td>
<td>Reporting period dates (Treatment, AEs)</td>
</tr>
<tr>
<td>PK/ADA collection data (Treatment)</td>
<td>Treatment doses and dates (Treatment)</td>
</tr>
<tr>
<td>Reporting period dates (Treatment, AEs)</td>
<td>Adverse event dates (AE: Report)</td>
</tr>
<tr>
<td>Dosing units (Treatment)</td>
<td>Lab dates (Laboratory Values)</td>
</tr>
<tr>
<td>Lab value units (Laboratory Values)</td>
<td>Lab value units (Laboratory Values)</td>
</tr>
<tr>
<td>Source documentation upload</td>
<td>Source documentation upload</td>
</tr>
</tbody>
</table>

- Rave also generates queries for missing information
  - Important to wait until the end of a cycle to enter data
Centralized Monitoring Component

• Source documentation submission for *(typically)* the first two patients randomized
  ◦ Requires the upload of auditable source documents into a Source Document Verification (SDV) form in Rave
  ◦ Examples of documents included in the review are:
    • Signed Informed Consent
    • Specimen Submission documentation
    • First two courses of treatment and adverse event source documents

• Monitors also review timeliness of data submission in Rave
Helpful Resources

- Your SWOG Data Coordinator!
  - S1400question@crab.org
  - MelanomaQuestion@crab.org
  - (206) 652-2267

- Auditors & monitors – here to help!

- Documents available on the protocol page at SWOG.org and CTSU.org

- Reports and Data Quality Portal (DQP)
S1404: A Phase III Randomized Trial Comparing Physician/Trial Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma

- Activated 10/15/15
- Accrual Goal of 1,378
  - 1,036 patients have been registered to Step 1
  - 934 patients have been randomized to Step 2
S1404 PD-L1 Tissue Requirement

• Local Pathology Review Form
  ◦ Tissue submission is a requirement, so this form must be completed and signed prior to Step 1 Registration

• Shipping Requirements
  ◦ 5 Unstained Slides – blocks are not accepted
  ◦ Slides must be shipped refrigerated, NOT ambient
  ◦ ID on the slides must match exactly the ID on either the pathology report or Local Pathology Review Form

• Additional Questions to complete in the Specimen Tracking System
S1404 Medical History Form

- Collects information about patient’s medical history prior to the start of treatment
- All conditions should be reported, even if deemed not clinically significant
- Unknown days and months are acceptable; however a valid year is required
  - A non-conformant error is generated if the year is unknown
  - Reminder: non-conformant errors prevent data from being submitted, which results in overdue expectations!
S1404 Medical History Form

Collection Date of Medical History: 15 Feb 2016

Does the patient have any medical history to report? Yes

**Enter all relevant medical history below. If the condition is present at the time of registration, please indicate that it is “Ongoing”. Explain any missing dates in the comments section.**

<table>
<thead>
<tr>
<th>#</th>
<th>Verbatim Term</th>
<th>Start Date</th>
<th>Stop Date</th>
<th>Ongoing?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Type II Diabetes</td>
<td>1 Mar 2007</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>2</td>
<td>Heart Murmur</td>
<td>UN UNK 2000</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>3</td>
<td>COPD</td>
<td>Entry Error</td>
<td>UN UNK</td>
<td>✓</td>
</tr>
</tbody>
</table>

Add a new Log line Inactivate
S1404 Adverse Event Reporting

- Extra fields on the AE Report form to capture additional data
  - Onset and Resolution dates
  - Action Taken
  - Outcome
  - Immune Related?
  - Treatment Received?
  - AdEERS Report Ticket Number

- Onset and Resolution date correspond to the specific grade, not the AE overall
### S1404 Adverse Event Reporting

#### Instructions:
- Report adverse events occurring up until the next cycle of treatment begins.
- If an adverse event changes grade during the reporting period, report each grade as a separate event. If an adverse event resolves and then recurs at the same or different grade, report each event separately.
- To report ongoing adverse events, provide the AE start date and mark the AE as “ongoing” on each eCRF until the event is resolved. On the last cycle that the AE is seen, provide the AE end date.
- Do not code a condition existing prior to registration as an adverse event unless it worsens.
- Indicate if the adverse event results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
- Submit the Concomitant Medications form documenting treatment received for any immune-related adverse events.
- Follow instructions in Section 16.0 of the protocol for expedited reporting requirements on this study.
- Record any expedited adverse events that were reported using Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). If the AdEERS report was amended, please amend the data on this adverse event form.
- Category lists may not include all adverse events from that category.

<table>
<thead>
<tr>
<th>#</th>
<th>Verbatim term</th>
<th>CTC adverse event term</th>
<th>CTC grade</th>
<th>CTC AE grade</th>
<th>Onset date</th>
<th>Resolution date</th>
<th>Action taken</th>
<th>Outcome of AE</th>
<th>Hospitalization (at least 24 hours)</th>
<th>Is the AE immune-related?</th>
<th>Treatment received for this AE?</th>
<th>AdEERS Report Ticket Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fatigue</td>
<td>Fatigue</td>
<td>1</td>
<td>Probable</td>
<td>6 Oct 2015</td>
<td></td>
<td>Dose Not Changed</td>
<td>Not Recovered/Not Resolved</td>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Anemia</td>
<td>Anemia</td>
<td>2</td>
<td>Probable</td>
<td>6 Oct 2015</td>
<td>7 Dec 2015</td>
<td>Dose Not Changed</td>
<td>Recovered/Resolved</td>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Anemia</td>
<td>Anemia</td>
<td>4</td>
<td>Probable</td>
<td>7 Dec 2015</td>
<td></td>
<td>Drug Withdrawn</td>
<td>Not Recovered/Not Resolved</td>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
S1404 Concomitant Medication Form

- Designed to capture any non-protocol medications a patient takes while on treatment
- General concomitant medication form that is present at Step 2 Randomization
- AE-specific concomitant medication forms also generate when it’s indicated that treatment is received for an immune-related adverse event
## S1404 Concomitant Medication Form

**Instructions:** Please complete if patient receives any non-protocol therapy. If patient received a glucocorticoid to treat immune-related adverse events, record the dose and start and stop dates of the initial high dose and start and stop dates of the steroid taper on separate lines. List each medication on a separate line, even if given concurrently. If patient stops a medication and then restarts at a later date, list each occurrence on a separate line.

<table>
<thead>
<tr>
<th>#</th>
<th>Concomitant Agent Name</th>
<th>Start Date</th>
<th>Stop Date</th>
<th>Ongoing</th>
<th>Dose</th>
<th>Units of Measure</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prednisone</td>
<td>1 Mar 2016</td>
<td>5 Mar 2016</td>
<td></td>
<td>40</td>
<td>mg</td>
<td>Oral</td>
</tr>
<tr>
<td>2</td>
<td>Prednisone</td>
<td>6 Mar 2016</td>
<td>8 Mar 2016</td>
<td></td>
<td>20</td>
<td>mg</td>
<td>Oral</td>
</tr>
<tr>
<td>3</td>
<td>Prednisone</td>
<td>9 Mar 2016</td>
<td>11 Mar 2016</td>
<td></td>
<td>10</td>
<td>mg</td>
<td>Oral</td>
</tr>
</tbody>
</table>

Add a new Log line Inactivate
S1400: A Biomarker-driven Master Protocol For Previously Treated Squamous Cell Lung Cancer (Lung-MAP)

*Biomarker-driven sub-studies (like S1400G) will progress to Phase III if study meets endpoint and Phase III is feasible, at which point the standard of care arm will be determined.
S1400 Tissue for Biomarker Profiling

- **S1400 Local Pathology Review Form**
  - Must be signed by local pathologist confirming adequate tumor content (both % tumor cells and total tumor volume)
  - Availability of adequate tissue is an eligibility requirement, so this form must be completed prior to registration

- Tissue shipment required within one working day following registration

- Use SWOG Specimen Tracking as usual
S1400 Resources & Where to Find Them

- Site Coordinators Committee
  - ORP Open Forum later today
  - LungmapSCC@crab.org
- “Your Institution's Lung-Map Status Update”
  - Emailed quarterly to your institution’s head CRA
- Examples of Beacon builds, sample source documents
  - On the protocol abstract page, under “S1400 Resources”
- Rave Data Entry Guidelines
  - Chapter 16e of the ORP Manual or as a link on the protocol abstract page
S1400 Rave Data Entry Guidelines

S1400 Screening Forms

Follow-up Tumor Assessment Form

Source Documentation: Follow up – Follow-up Tumor Assessment Form

Scan reports must be uploaded to RAVE in addition to submitting the scan(s) within 7 days to TRAD per Section 15.
S1400 at the Group Meeting

- ORP Open Forum
  - Thursday 12:30 pm, in Pacific NO (Pacific Level)
  - Look for the **S1400 Lung-MAP Site Coordinators Committee** table

- S1400 Lung-Map Update Meeting
  - Friday 2:30 pm, in Seacliff A-D (Bay Level)

Come say hi!
Thank you!