# Navigating Alliance Protocols

## Where to Find it and Whom to Contact

Michael Kelly, MA
Director of Protocol Operations
Alliance 2016 Group Meeting

# Alliance Model Protocol History

- Alliance for Clinical Trials in Oncology founded February 2011
- Consensus protocol template created by protocol staff members from each legacy group (ACOSOG, NCCTG, and CALGB)
- Opportunity to start afresh and incorporate successful components of legacy group protocols
- All new *concepts* developed after Spring/Summer 2013 would utilize Alliance model protocol
- Alliance model protocol approved by Alliance Central Operations Office, Statistics and Data Center, Translational Research Program, and all Alliance committee chairs and vice chairs.

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# Alliance Model Protocol Template

- Chronologically, patient management workflow-based
  - Rationale and objectives for study
  - Patient selection and enrollment
  - Patient scheduling, data and specimen submission
  - Treatment and dose modifications including ancillary therapy
  - End of treatment
  - Analysis
- Template undergoes quarterly review by Alliance Operations, Statistics and Data Center, Oncology Nursing, and CRP staff representatives

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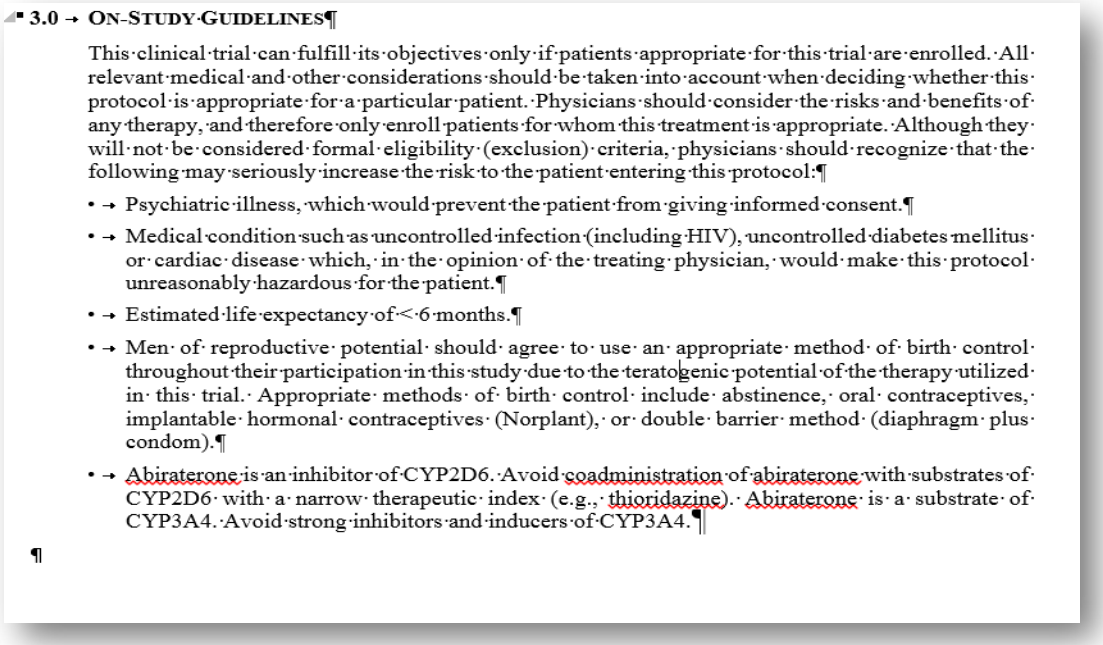
# Approaches – Patient Selection (On Study Guidelines)

- Intended to provide guidance about the appropriateness of individual patients for protocol therapy
- Includes items often not verifiable at time of audit (e.g., life expectancy, ability to swallow oral formulations, birth control)
- **Not** strict eligibility criteria



3.0 ON-STUDY GUIDELINES

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate. Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness, which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Estimated life expectancy of < 6 months.
- Men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives (Norplant), or double barrier method (diaphragm plus condom).
- Abiraterone is an inhibitor of CYP2D6. Avoid coadministration of abiraterone with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). Abiraterone is a substrate of CYP3A4. Avoid strong inhibitors and inducers of CYP3A4.

# Approaches – Patient Selection (Eligibility Criteria)

- Study chairs may *interpret* how individual patients meet eligibility criteria, but they may NOT issue waivers.
  - "This is (or is not) a complete resection," or "this does (or does not) qualify as prior therapy," etc.
- Eligibility criteria contain both inclusion and exclusion criteria. No separate inclusion/exclusion criteria which may lead to confusion.

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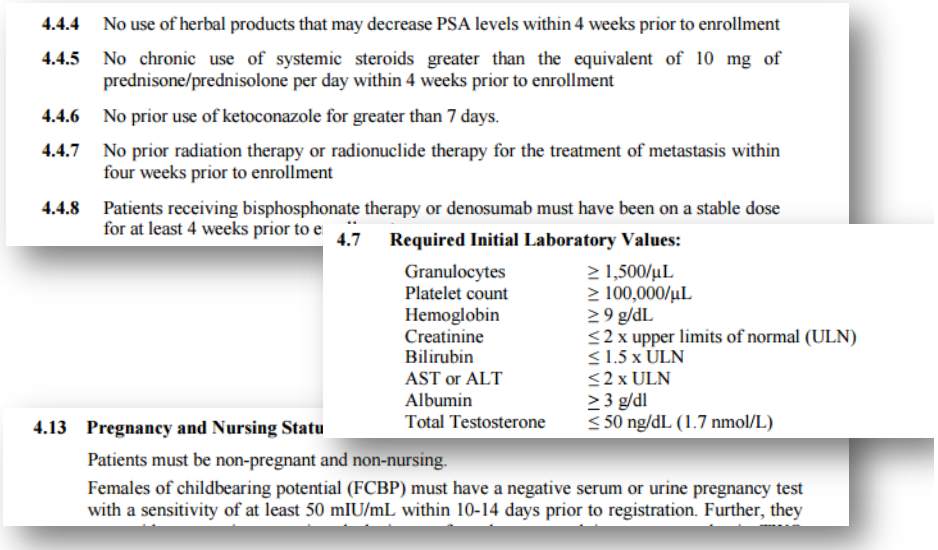
# Approaches – Patient Selection (Eligibility Criteria)

- Protocols specify when, relative to registration, tests must have been performed
  - If the time frame is part of the eligibility criterion, both the test result ***and*** the time frame must be in the acceptable range
  - If the time frame is not part of the eligibility criterion, then the test result (not the date) must be in the acceptable range
  - Out of range times that are not part of eligibility criteria are protocol deviations. Decisions to assign audit deficiencies will occur at time of audit with full case review
  - Please contact Study Chair **<u>and</u>** Protocol Coordinator with questions (email preferred)



**4.4.4** No use of herbal products that may decrease PSA levels within 4 weeks prior to enrollment

**4.4.5** No chronic use of systemic steroids greater than the equivalent of 10 mg of prednisone/prednisolone per day within 4 weeks prior to enrollment

**4.4.6** No prior use of ketoconazole for greater than 7 days.

**4.4.7** No prior radiation therapy or radionuclide therapy for the treatment of metastasis within four weeks prior to enrollment

**4.4.8** Patients receiving bisphosphonate therapy or denosumab must have been on a stable dose for at least 4 weeks prior to e

**4.7 Required Initial Laboratory Values:**

| | |
|---|---|
| Granulocytes | ≥ 1,500/μL |
| Platelet count | ≥ 100,000/μL |
| Hemoglobin | ≥ 9 g/dL |
| Creatinine | ≤ 2 x upper limits of normal (ULN) |
| Bilirubin | ≤ 1.5 x ULN |
| AST or ALT | ≤ 2 x ULN |
| Albumin | ≥ 3 g/dl |
| Total Testosterone | ≤ 50 ng/dL (1.7 nmol/L) |

**4.13 Pregnancy and Nursing Statu**

Patients must be non-pregnant and non-nursing.

Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10-14 days prior to registration. Further, they

# Approaches – Patient Selection (Eligibility Criteria)

- No such thing as a *prospective* waiver. We cannot give permission to deviate from the protocol. If the protocol were not to be followed:
  - Document the reason in the patient chart
  - Reflect the deviation from protocol on the study forms
  - Make sure all source documentation (copies of emails, notes regarding telephone calls, etc.) are available for audit
  - Follow any local IRB and institutional policies regarding notification
- Alliance does not require submission or approval of deviations (exceptions include dosing errors)
- All eligibility criteria within Alliance protocols undergo review by an Alliance Executive Officer (a medical oncologist)

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# Approaches – Study Calendar (Part 1)

- *Pre-study* testing intervals in study calendar are intended as guidelines. Individual tests/procedure dates outside these intervals may be considered protocol deviations, but may be discussed with Study Chair **and** Protocol Coordinator. Please retain any study team correspondence in patient records for review at time of audit.
- *Testing requirements in the study calendar are the minimum expectations.* During treatment laboratory and clinical parameters are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician.
- Days = calendar days unless otherwise specified.

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# Approaches – Study Calendar (Part 2)

- Study calendar may make references to specimen collection, but schedule and details about procurement, handling and shipment appear in the dedicated specimen submission section.
- Symbols (e.g., “*”, “**”, “†”, etc.) are used for footnotes for column headers.
- Numerals (e.g., “(1)”, “(2)”, “(3)”, etc.) are used within the calendar for tests/procedures requiring further explanation
- Letters (eg., “A” “B” “C”, etc.) are used within the calendar for tests that vary slightly from the schedule in the column header.

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# Approaches – Study Calendar (Part 3)

- Where permissible, newer Alliance protocols include windows for tests and observations in studies.
- Missing a scheduled day of treatment for other than protocol-specified dose adjustments (Memorial Day, July 4th, New Years', etc.) is sometimes unavoidable. Document, document, document….

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# Approaches – Data and Specimen Submission

- Data submission schedule is included in paper case report form packet.
  - Paper CRF packet available on Alliance web site
  - Paper CRFs are intended for reference not for submission
  - All specimen procurement, processing and submission instructions are provided in a *single* section


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# Treatment Plan & Dose Modifications

- Treatment
  - Alliance policy requires treatment must begin within 7 days after registration, unless otherwise specified in the protocol.
  - Organized chronologically by treatment modality
- Ancillary Therapy, Dose Modifications, and Unblinding
  - Includes supportive care and other considerations
  - Dose modifications are organized by system, organ and class
  - Emergency unblinding included in all blinded studies
  - Planned unblinding (progression, # of cycles) included when allowable

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# Removal of Patients from Protocol Therapy

- Specifies duration of protocol treatment and steps to follow after discontinuation of therapy.
- **Follow-up for ineligible patients who continue with protocol treatment**
- **Follow-up for ineligible patients who discontinue protocol treatment**
- **Follow-up for patients who are registered, but who never start study treatment**
- Future Alliance trials will provide additional detail about specimen and quality of life submission requirements for patients who discontinue protocol treatment.

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# Expedited Adverse Event Reporting

- Serious adverse events must be reported using CTEP-AERs
- Minimum reporting guidelines in NCI-supplied, FDA required SAE tables

**ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

| Hospitalization | Grade 1 Timeframes | Grade 2 Timeframes | Grade 3 Timeframes | Grade 4 & 5 Timeframes |
|---|---|---|---|---|
| Resulting in Hospitalization ≥ 24 hrs | 10 Calendar Days | | | 24-Hour; 5 Calendar Days |
| Not resulting in Hospitalization ≥ 24 hrs | Not required | | 10 Calendar Days | |

**NOTE**: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

- To streamline reporting for institutions and sponsors, in addition to the SPEER, a list of reporting exclusions is provided
- Additional reporting instructions for AEs may be included.
- Both the table and reporting exceptions should be considered together when determining reporting requirements

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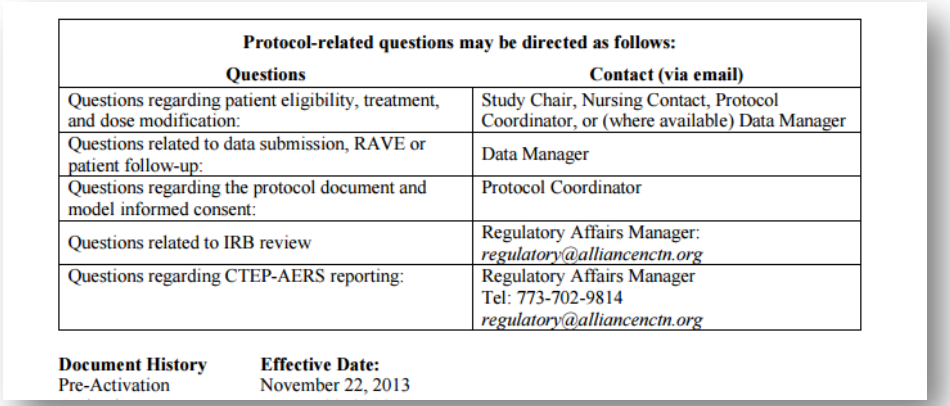
# Protocol Resources & Question Triage

- Study chairs are primarily responsible for answering questions, usually regarding clarification of eligibility requirements, treatment or dose modifications
- Study co-chairs also may answer questions, especially if treatment modality related
- Nurse Oncology liaisons may assist in answering nursing related questions
- Pharmacy Liaisons may assist in answering agent administration instructions
- To help ensure timely response, please copy protocol coordinators



**Protocol-related questions may be directed as follows:**

| Questions | Contact (via email) |
|---|---|
| Questions regarding patient eligibility, treatment, and dose modification: | Study Chair, Nursing Contact, Protocol Coordinator, or (where available) Data Manager |
| Questions related to data submission, RAVE or patient follow-up: | Data Manager |
| Questions regarding the protocol document and model informed consent: | Protocol Coordinator |
| Questions related to IRB review | Regulatory Affairs Manager: *regulatory@alliancenctn.org* |
| Questions regarding CTEP-AERS reporting: | Regulatory Affairs Manager<br>Tel: 773-702-9814<br>*regulatory@alliancenctn.org* |

**Document History** **Effective Date:**
Pre-Activation November 22, 2013

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# What's NOT in protocol documents, but does appear on study specific web pages…

- Drug order instructions and drug order forms
- Study funding information
- Rave forms and data submission schedule
- Patient-directed materials (eg, handouts, brochures)

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# A few words about ….

- Protocol appendices
  - Reduce protocol appendices to avoid potential for discrepancies
- Patient Questionnaire Booklets
  - Need to order prior to first patient
    - From Mayo for studies available to Alliance only
    - From CTSU for Alliance studies available to NCTN/NCORP on CTSU
  - Only questionnaires not in booklets may be provided to patients. Other measures in protocol appendices are provided for IRB approval only, and are not intended to be provided to patients.
  - Some exceptions include neurocognitive exam booklets for both patients and certified examiners

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# A few words about ….

- Amendments
  - Overall attempt to limit number of amendments to no more than twice per year per study
  - Amendments distributed via Alliance Bi Monthly Posting (1st & 15th of each month)
  - Alliance Audit monitoring based on Alliance Bi Monthly posting dates (and not CTSU)
- Protocol development
  - Protocol development occurs with representation from members of the Oncology Nursing Committee, Clinical Research Professionals Committee, Pharmacy Committee, and Patient Advocates in addition to the study team
  - Protocol and forms development occur with input of Alliance Executive Officers (medical oncologists and researchers with discipline expertise)

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# A few words about…

- Alliance Bi Monthly Study Status Sheet
  - All Alliance protocols in development and active studies listed on Alliance web page under Protocol Listing in Alliance Status Sheet. Current amendment listed for active studies, and protocol closures, suspensions, and activations for calendar year identified.

**PROTOCOLS AND CONCEPT SHEETS PENDING - May 1, 2016**

| Number | Status | Study Short Title | Phase | Study Chair |
|---|---|---|---|---|
| | | **BREAST COMMITTEE** | | |
| A011401 | P/po | Role of weight loss in adj tx | III | J. Ligibel |
| A011502 | P/NCI | Asprin adj tx node+ | III | W. Chen |
| | | **EXPERIMENTAL THERAPEUTICS COMMITTEE** | | |
| A091404 | PA | Enzal for pts w/ androgen rec+ salivary ca | II | A. Ho |
| A091502 | SCRC | Reversing resistance to pazopanib w/ histone deacetylase inhib | II | D. Munster |
| A091602 | C/NCI | Adj anti-PD-1 tx in pts w/ high risk stage IB-IIC melanoma | II | L. Geskin |

**ACTIVE ALLIANCE PROTOCOLS - May 1, 2016**

| Number | Study Short Title | Phase | Study Chair | Activated |
|---|---|---|---|---|
| | **BREAST COMMITTEE** | | | |
| A011104-05 | Preop Br MRI on surg outcomes, costs, and QOL of women w/BrCa | III | I. Bedrosian | 02/21/14 |
| A011106-04 | Alt approaches clin stg II & III ER+ BrCa (ALTERNATE) | III | C. Ma | 12/13/13 |
| A011202-05 | Eval of axill LN dissect in BrCa pts w/+ SLN Dz post neoadj chemo | III | J. Boughey | 02/07/14 |
| A011203-02 | Breast Z Endoxifen | III | M. Goetz | 03/06/15 |
| Z11102-06 | Breast conservation surgery | II | J. Boughey | 07/23/12 |
| CTSU | S1207: Rand plcb cont end tx +/- everolimus HR+ HER2- br ca | III | M. Goetz | 09/03/13 |
| | **EXPERIMENTAL THERAPEUTICS COMMITTEE** | | | |

**RECENT ALLIANCE PROTOCOL CLOSURES**
(in order of closure date)

| Number | Study Short Title | Study Chair | Activated | Closed |
|---|---|---|---|---|
| CTSU | S0819: Carbo/taxol +/-bev w/ or w/out cetux in adv. NSCLC | S. Herbst | 07/22/09 | 05/01/15 |
| CTSU | E5508: Maint tx w/ bev, pemetrexed or both for Adv Non-Squam NCSLC | S. Ramalingam | 07/30/12 | 05/08/15 |
| 80803-05 | PET scan-directed combined modality therapy in esophageal cancer | K. Goodman | 07/15/11 | 05/11/15 |
| A051103-04 | Ph I rituximab, lenalidomide, and ibrutinib in prev untd follic lymph | C. Ujjani | 06/21/13 | 05/11/15 |

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# Questions

- Suggestions for the model protocol template may be directed to mkelly1@uchicago.edu
- Individual protocol questions may be directed to protocol coordinators identified on protocol cover pages

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