



National Cancer Policy Forum Workshop on Multi-Center Phase 3 Clinical Trials and NCI Cooperative Groups

Session 3: Data Collection Standards to Establish Safety and Efficacy: How Much Data Is Enough?

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NCI Cooperative Group Program

- Experienced, independent, cancer clinical trials organization
- Track record of high-quality research
- Well-established, publicly available/reviewed procedures for
 - Data management & monitoring
 - On-Site Auditing
 - On-going Educational Programs
- On-going educational programs

NCI/CTEP-sponsored Group Trials Supporting FDA-approved Indications for New Agents

- **2001**
 - Imatinib mesylate (COG, SWOG) – CML
- **2002 -2003**
 - FISH probe for her2/neu (PathVision™) – breast cancer
 - Multigene Oncotype Dx™ Assay – breast cancer
- **2004**
 - Letrozole (NCIC, Intergroup) – breast
 - Oxaliplatin (NCCTG, Intergroup) - colon
 - Taxotere (SWOG) – breast
 - Nelarabine (COG) – leukemia
- **2006**
 - Bevacizumab (ECOG, Intergroup) – colon, lung
 - Trastuzumab (NSABP, NCCTG, Intergroup) – breast
- **2008**
 - Bevacizumab (ECOG, Intergroup) - breast

High Priority Ongoing Trials: Supporting Potential Supplemental Licensing Indications

- **E2805:** A Randomized, Double-Blind Phase 3 Trial of Adjuvant Sunitinib vs. Sorafenib vs. Placebo in Resected **Renal Cell Carcinoma** (Reviewed by FDA Prior to Activation – Actively Recruiting)
- **E1505:** Phase 3 Randomized Trial of Adjuvant Chemotherapy With or Without Bevacizumab for Patients With Completely Resected Stage IB-III A **Non-Small Cell Lung Cancer** (Reviewed by FDA Prior to Activation – Actively Accruing)
- **S0518:** Phase 3 Randomized Comparison of Depot Octreotide Plus Interferon Alpha vs Depot Octreotide Plus Bevacizumab in Advanced, Poor Prognosis **Carcinoid** Patients (Reviewed by FDA Prior to Activation – Actively Recruiting)

Review of Cooperative Group Phase 3 Trials at Concept Stage by FDA

- **Early identification of phase 3 trials in which companies are definitely interested in licensing**
 - Process for rapid concept review by FDA within 21 days (and subsequent SPA) agreed to interagency internal SOP in February 2006
- **FDA given opportunity to review & comment on phase 3 trials at concept stage if there is a potential licensing indication even if company has not formally expressed an interest in a licensing indication**
 - All concepts with IND agents sent to FDA
 - Groups may proceed with developing the protocol after CTEP approval but are aware that the FDA may offer comments requiring a response

NCI Cooperative Group Program: Major Issues For Discussion In Session

- Data management
- Data collection
- Adverse event reporting and monitoring
- Auditing
- Verification of trial endpoints
- Interim analyses

Is it appropriate or desirable for NCI-supported clinical trials to be performed according to current industry practice?

- **Data Management Guiding Principles**

Collect only necessary information – streamlined for collection of most important study data based on background of existing information on agents & treatments

- Important eligibility criteria (Pathology, Operative Reports, Imaging Reports, Tissue/Biomarkers)
- Patient baseline characteristics
- Treatment Delivery
- Adverse Events
- Study Outcomes
- Additional information

NCI Cooperative Group Data Mgt / Monitoring

- **Data Management Guiding Principles**

On-going monitoring of quality, completeness, and internal consistency of data as well as timeliness of submission

- Case report forms & associated queries are official record of communication between Group and site
- Group SOPs for trial conduct address required elements in protocol that are verified at audit
- Ongoing education of Group staff, site CRAs and physicians
- Data Safety and Monitoring Boards for all Phase 3 trials

Streamlined Data Collection: Current Practice

- **Data Collection Streamlined Based on Existing Information Available for Agents & Treatments**
 - Review of case report forms by FDA pre-activation
 - Eligibility: Checklist or collection of sub-set of data on select eligibility criterion
 - Treatment & Dose Modifications: Collection of non-protocol and subsequent treatment when feasible & important, but not required
 - Concomitant Medications: Collection on select concomitant medications that are of interest given specific protocol therapy
 - Design/Outcome: Blinding, central review in select cases, detailed pre-specified analysis plans

Streamlined Data Collection – Adverse Events

- **Routine Collection Adverse Events (AEs)**
 - **Routinely collect Grades 3-5 for AEs in phase 3 trials**
 - Consider expansion of standard collection for a “new” combination in subset of patients & for selected AEs only when there is very little safety information available and specific rationale exists to support more extensive collection
 - **Extensive data collection on sub-set of patients only if needed**
 - More extensive data collection on some type of AEs (e.g., Cardiac, HTN, Hepatic)

Streamlined Data Collection – Lab Values & AEs

- **Laboratory values & AEs collected but not routinely reported per protocol schedule or at time of dose modification to streamline process**
 - Selected lab values collected at baseline & at certain time-points (e.g., LFTs for agent known to be associated with hepatotoxicity in an adjuvant trial), but lab values not reported routinely per study calendar unless specifically required

Intensive Monitoring for Serious AEs via Expedited Reporting System

- **Phase 3 trials include expedited AE reporting guidelines so that CTEP can monitor safety of investigational agents in an extensive clinical trial network and adequately capture safety data that are clinically significant and relevant in a timely fashion**
- **For all Group trials, AEs are reported through two mechanisms**
 - **CRFs:** Routine AE reporting for all AEs
 - **AdEERS** (Adverse Event Expedited Reporting System): Expedited reporting for a subset of AEs that are serious and/or unexpected; evaluated centrally

Intensive Monitoring for Serious AEs via Expedited Reporting System

- **CTEP's expedited reporting system for serious adverse events (AdEERS) monitoring standards exceed FDA's requirements, and provides more detailed information for safety review in an expedited fashion so serious safety signals may be picked up more quickly. All these AEs are also required to be submitted on the routine AE case report forms as well.**
- **However, the AdEERS system is an enhancement to routine collection of AEs (i.e., allows serious AEs for the investigational arms to be reported quickly), but it is used as a supplemental to the safety review for the trial only. The Group's database of all AEs contains the complete safety record for the trial.**

NCI Cooperative Group On-Site Audit Program

- Audit program based on institutional performance under a Principal Investigator for Cooperative Group at that site
- Auditing program is a independent review process with an educational component
- NCI standard guidelines for conduct of audits & requires all Coop Group institutions be audited at least once every 36 months but all sites at risk for audit at any time (e.g., special audits); Phase I/II sites audited every six months
- Clinical Trials Monitoring Branch (CTMB) at NCI/CTEP has direct oversight responsibility for the audit system
 - Conducts Co-site visits on about 10% of all audits
 - CTMB Auditing Guidelines publicly available at:
<http://ctep.info.nih.gov/monitoring/guidelines.html>

NCI Cooperative Group On-Site Audit Program

- **Group Selection of Cases for Audits**
 - Random selection of at least 10% of patients cases for site during the 3-year period (usually more than 10%)
 - Selection can be supplemented for IND studies; low accrual (all pts audited), past performance, investigational treatment arm, etc.
 - Selection made with NO knowledge of pt case outcome
 - All sites undergo certain # of “unannounced” audits
 - Lead Group for intergroup study selects cases; a Group performs CTSU audits of their members who participate in other Groups’ studies
- **Group Audit Team**
 - Group volunteer auditors, usually 2 to 4, make up audit team
 - Group has training requirements for auditors & service requirements
 - Regular feedback among auditors (Audit Committee) and to the Group Stats Office (& CRA Committee / Nursing Committee)

NCI Cooperative Group Program: On-Site Audits & Patient Case Review Categories

- Time Period: 01/01/1999 thru 6/30/2006
- Total # of Audits = 8,512
- Total # of Patient Cases = 63,363
- All Group Treatment Trials Plus STAR & SELECT

<u>Patient Case Review Categories</u>	<u>% Pts Audited with Major Deficiency</u>
• Informed consent	4.4%
• Eligibility	5.4%
• Treatment	6.8%
• Adverse Events	2.3%
• Disease Outcome/Response	3.7%
• General Data Timeliness	7.6%

What is the standard against which to compare these data?

NCI Cooperative Group On-Site Audit Program

Patients Audited as of June 30, 2006 on
NCI Cooperative Group Audits

For Studies Activated Between 1999 and 2003

Category	# Pts Accrued	# Pts Audited	% of Accrued Pts Audited
All Phase 3 Coop Grp Treatment Trials	108,867	17,840	16.4%
All Phase 3 “CTEP IND” Coop Grp Treatment Trials	21,908	4,727	21.6%

NCI Cooperative Group Program - On-Site Audits Assessment of 10% Case Selection Minimum

**% Patients with Major Deficiencies in Patient Case Review Categories
as the Number (%) of Patients Audited for a Group of Trials Increases**

For All Adult Phase 3 Treatment Trials Activated in 2000

Year	Cum. Pt Accrual	% Pts Audited	% Pts with MD in Eligibility Category	% Pts with MD in Treatment Category	% Pts with MD in Outcome Category	% Pts with MD in Toxicity Category	% Pts with MD in Data Timeliness
2000	1,548	1.2%	0.0%	0.0%	0.0%	0.0%	0.0%
2001	6,516	3.9%	2.8%	1.2%	0.8%	2.0%	2.4%
2002	11,345	6.7%	3.6%	5.9%	0.9%	2.0%	5.0%
2003	14,821	12.3%	3.7%	7.6%	1.5%	1.9%	4.7%
2004	17,430	16.5%	4.1%	7.2%	1.3%	2.3%	4.6%
2005	18,463	20.0%	4.1%	7.6%	1.4%	2.3%	4.7%
2006	18,628	21.0%	4.2%	7.5%	1.5%	2.3%	4.8%

NCI Cooperative Group On-Site Audit Program

- FDA “Audit Certificate” Listing has been provided for Group trials used to support licensing indications
 - “Audit Certificate” provided by industry verifies that site was audited and gives date of audit
 - Summary Audit Report for Group
 - List of All Institutions Participating in Trial with Date of Last Audit by Credited Group
 - Any sites receiving “For Cause” audits or whose membership status was terminated can be identified for FDA Audit Listing, if required
 - Verification by NCI/CTEP and Lead Group for trial

Verification of Clinical Trial Endpoints

- Historically, most Group Phase 3 Trials have had overall survival or disease-free survival as primary endpoint
- Non-survival primary endpoints may introduce new issues regarding verification
 - Investigator-assessment of endpoint performed by large network of investigators across the country in a randomized trial (as opposed to Central independent review)
 - Trial design modified to blinded treatment when feasible and appropriate
 - Central review already performed for certain data elements (e.g., pathology review)
 - CTEP committed to investigating collection of radiographic images for central review when required for scientific/medical assessment

VIEW (Virtual Imaging Evaluation Workspace)

- Allow for independent verification of imaging responses that is timely, reliable, and affordable for certain trials / endpoints (e.g. PFS)
 - Although blinded independent central review (BICR) may lessen some potential biases, it does not remove all bias from evaluations of treatment effectiveness -- it may introduce bias because of informative censoring which results from having to censor unconfirmed locally determined progressions.
 - Double-blinded trials with consistent application of measurement criteria are the best means of ensuring unbiased trial results.
 - When such designs are not practical, BICR is not recommended as a general strategy for reducing bias. However, it may be useful as an auditing tool to assess the reliability of marginally positive results.*
 - VIEW provides infrastructure to conduct BICR with standard collection of images and independent review of images for Cooperative Group trials. NCI feels this can be a useful quality control procedure to exclude systematic bias.

**Dodd L et al, JCO, in press 2008*

Clinical Trial Endpoints: Independent Central Radiologic Review

	E2100				Lapatinib				2119G			
	Invest		RadRev		Invest		RadRev		Invest		RadRev	
	C	A	C	A	C	A	C	A	C	A	C	A
Median PFS (mo)	5.8	11.4	5.8	11.3	4.1	5.5	4.1	6.2	3.8	4.3	4.2	4.9
Differences in PFS by different review Methods (mo)	5.6		5.5		1.4		2.1		0.5		0.7	
Hazard Ratio	0.42		0.48		0.69		0.55		0.92		0.96	

Operational Plan for Interim Analyses

- Interim Analyses specified prospectively in the protocol
- Group Data Safety Monitoring Boards overseeing Phase 3 trials meet every 6 months
- Interim Analyses (IA) are event-driven with medical review confirmation of events
 - Data-set locked at specific time point prior to the DSMB meeting
 - Group-wide effort to update data collection on all elements prior to analysis / presentation to DSMB
 - Associated data collection (e.g., adverse events) may not be final for patient data-set locked based on events
- Process for managing data-set at time of IA, especially when trial is stopped and may have licensing implications

Future Enhancements to the Group Trials Network

- Modify the expedited adverse event reporting system into a more user-friendly and expanded system (CARES) that will allow translation of CTCAE terms to MeDRA and allow reporting of verbatim descriptions of AEs in addition to CTCAE/MeDRA terms
- Implementation of a Remote Data Capture system across the Group system in the near future will allow more standardization across the system, will improve timeliness of data reporting as well as quality assurance programs
 - Built in error checks
 - Standardized front end for NCI-supported clinical trials

NCI Cooperative Group Program: How Much Data Is Enough?

Data management
Data collection
Adverse event reporting and monitoring
Auditing
Verification of trial endpoints
Interim analyses

- ***It is neither appropriate nor desirable for NCI-supported clinical trials to:***
 - Collect data that is never used
 - Consider the only measure of adequate compliance to require monthly on-site source document checks
 - Utilize expensive verification procedures that themselves have not been verified
- ***100% source verification is neither reasonable nor necessary***
 - Long history of FDA-approved indications have resulted from NCI-supported trials
 - Unclear what constitutes “proper monitoring” especially for PFS endpoints
 - Clearly, increased monitoring is very costly and does not indicate increased quality
- ***Face a critical requirement to maintain patient safety and data integrity while moving away from the current costly and inefficient model***

NCI/Industry Clinical Trials: Next Steps

GOALS:

- eCRF to enhance standardization is critical
 - Active input of industry, academics, and cooperative groups in development of both eRDC systems and eCRF as part of CTWG/caBIG initiative
 - Multiple eCRF modules near completion
- Free-up resources currently consumed by non-value added clinical trials processes to be used for the critical assessment of important scientific endpoints
- Urgent need to develop, for approval by the FDA, a standardized, and streamlined, approach to data management, data monitoring, auditing, and statistical evaluation of licensing trials supported by the NCI