Coping With Adverse Event Reporting

The Cancer Cooperative Group Experience

Outline of Talk

- Description of the North American cancer cooperative group system
- Regulatory roles of NCI's Cancer Therapy Evaluation Program (CTEP) and of the NCIC Clinical Trials Group (NCIC CTG)
- Adverse event management at NCIC CTG and CTEP
- Observations/Conclusions

Cancer Cooperative Groups

Cancer Cooperative Groups

- History
  - In the years immediately following the second world war, US cancer drug discovery and development was focused at the US National Cancer Institute
  - When intramural investigators began to leave NCI for academic institutions, programs were established to allow them to continue their research in an extramural setting
    - These programs evolved into the US cooperative cancer group system and were the basis for establishing an Investigational Drug Branch

Cancer Cooperative Groups

- Features of US system
  - Established networks of investigators and investigative sites allied to a coordinating centre or centres that provide (s) operational and statistical support
  - Receive ongoing core funding via the Cancer Treatment Evaluation Program (CTEP) for group activities
  - Currently undergoing major restructuring
- Similar, but not identical groups in Europe, Australia/New Zealand

Cancer Cooperative Groups

- One national group in Canada (NCIC CTG) funded primarily by Canadian Cancer Society, but also by NCI
  - Functions similarly to US groups, but has a single central office that provides operational and statistical support
  - Also differs from most US groups in having a cadre of academic physicians (physician coordinators) based at the central office

Regulatory Roles

CTEP

NCIC CTG

Regulatory Roles

- CTEP
  - Supplies drugs for cooperative group studies and for phase I/II studies done outside cooperative group mechanism
    - Originally most drugs from NCI drug development program, but now many come on contract from industry
  - When CTEP supplies drugs, it files IND and has the role of study sponsor
  - Currently, 100 open INDs

Regulatory Roles

- NCIC CTG
  - Files CTA and acts as sponsor for any of its own studies that involve investigational drug use
    - Because of Health Canada regulations, this represents virtually all drug studies

Regulatory Roles

- NCIC CTG
  - Also serves as Canadian sponsor for cooperative group studies originating outside of Canada in which NCIC CTG participates
    - Most, but not all, such studies originate in US facilitated by the Cancer Trials Support Unit (CTSU) mechanism
      - CTSU mechanism allows members of any NCI cooperative group to participate appropriate group led studies
        - Gives Canadian centres access to US studies, but NCIC CTG must sponsor in Canada
  - Currently, 115 open trials under a CTA

Adverse Event Management

NCIC CTG

CTEP

Adverse Event Management

- NCIC CTG
  - Volume
    - From 2004 through 2011, NCIC CTG received an average of 2300 "reportable" events yearly
      - About 25% of these were Serious Adverse Events (SAEs) from trials for which NCIC CTG held the CTA. The remainder were from sponsors of other trials using the same drugs (SUs)
  - Review
    - Every event reported to NCIC CTG are reviewed by one of the physician coordinators in the Group Central Office
    - Events that meet the criteria for regulatory reportability (serious, unexpected and related) are reported to Health Canada and distributed to sites (individually or in line listings)

Adverse Event Management

- NCIC CTG
  - Impact of review and trends

	# Received		% Distributed	
Year	SUs	SAEs	SUs	SAEs
2004	400	461	7%	0%
2005	536	538	15%	0%
2006	1073	563	27%	6%
2007	2712	488	14%	8%
2008	3501	419	10%	11%
2009	2159	532	6%	9%
2010	838	597	7%	5%
2011	614	699	10%	4%

Adverse Event Management

- CTEP
  - Volume
    - CTEP received 3813 SAEs on trials for which it held the IND in 2010 and 5053 in 2011
    - Also receive safety reports from external sponsors in approximately equal volume, but numbers are not tracked precisely
  - All SAEs and safety reports are reviewed by Senior Investigators in the Investigational Drug Branch
  - Events that meet the criteria for reporting to the FDA (now also serious, unexpected and related) are submitted as an IND safety report to the FDA and distributed to investigators

Adverse Event Management

- CTEP
  - Impact of review and trends

Time	#SAEs received	#SAEs submitted	% submitted
2010	3813	165	4.3%
2011	5053	218	4.3%
28/3/2011* – 16/4/2012	5704	203	3.6%

* Implementation of FDA Final Rule

Observations/Conclusions

Observations/conclusions

- The vast majority of adverse events submitted to the public sponsors of cancer trials in North American do not need to be reported to regulatory authorities
  - There appear to be two explanations for this:
    - Protocols often require ***all*** serious adverse events to be reported including those that are expected or unrelated
      - This issue can potentially be addressed at the time of study design
    - Pharmaceutical sponsors of other studies using the same drug must notify other sponsors of events they have received and reviewed
      - This issue is less controllable, but some efficiencies can be realized through negotiation
      - The use of line listings has reduced volume for NCIC CTG

Observations/conclusions

- If all events reported to sponsors were passed on to participating sites it would create an intolerable burden for site investigators and/or their IRBs/REBs
  - In fact, many ethics boards will now only accept reports of events that have an impact on study conduct (unanticipated problems)
- Until and if a way is found to reduce the volume of events reported to study sponsors some form of central review and filtering is clearly desirable

Observations/conclusions

- The systems in place at CTEP and NCIC CTG for adverse event management may provide a model that could be applied in other settings

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