

Data Safety Monitoring:

- * Why is it done?
- * How do you do it?

Bambi Grilley, RPh, RAC, CCRC, CCRP, CIP

Assistant Professor, Pediatrics
Director, Clinical Protocol Research and Regulatory Affairs
Center for Cell and Gene Therapy
Texas Children's Cancer Center

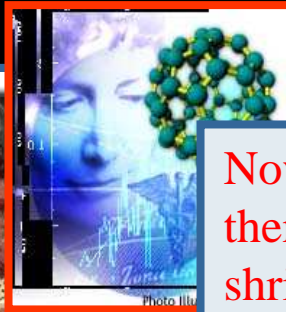
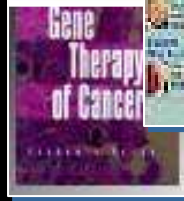
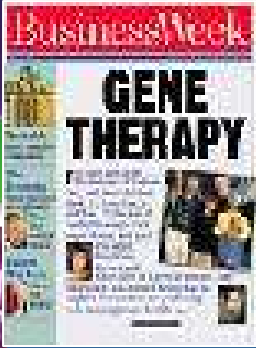
Baylor College of Medicine

Disclosure

- No financial relationships to disclose.

2 GENE THERAPY STUDIES HALTED; AIDS, HEPATITIS VIRUS CONTAMINATION OF ENGINEERED CELLS FEARED

Washington Post 03/09/2000



Stem cells grown outside the body
Feat could offer patients a ready supply of life-giving cells

Novel gene therapy shrinks tumors



Designer stem cells may make chemotherapy more tolerable

FDA STOPS RESEARCHER'S HUMAN GENE THERAPY EXPERIMENTS



WASHINGTON POST
Thursday, March 2, 2000

Definitions

- Data Safety Monitoring Plan (DSMP)
- Data Safety Monitoring Board (DSMB)
- Data Monitoring Committee (DMC)

Guidance

- 1979 Policy which included the concept that “every clinical trial should have provision for data and safety monitoring
- 1998 Policy on Data and Safety Monitoring released
- 2000 Further Guidance on DSMB released
- FDA Guidance released 2001, 2005, 2006

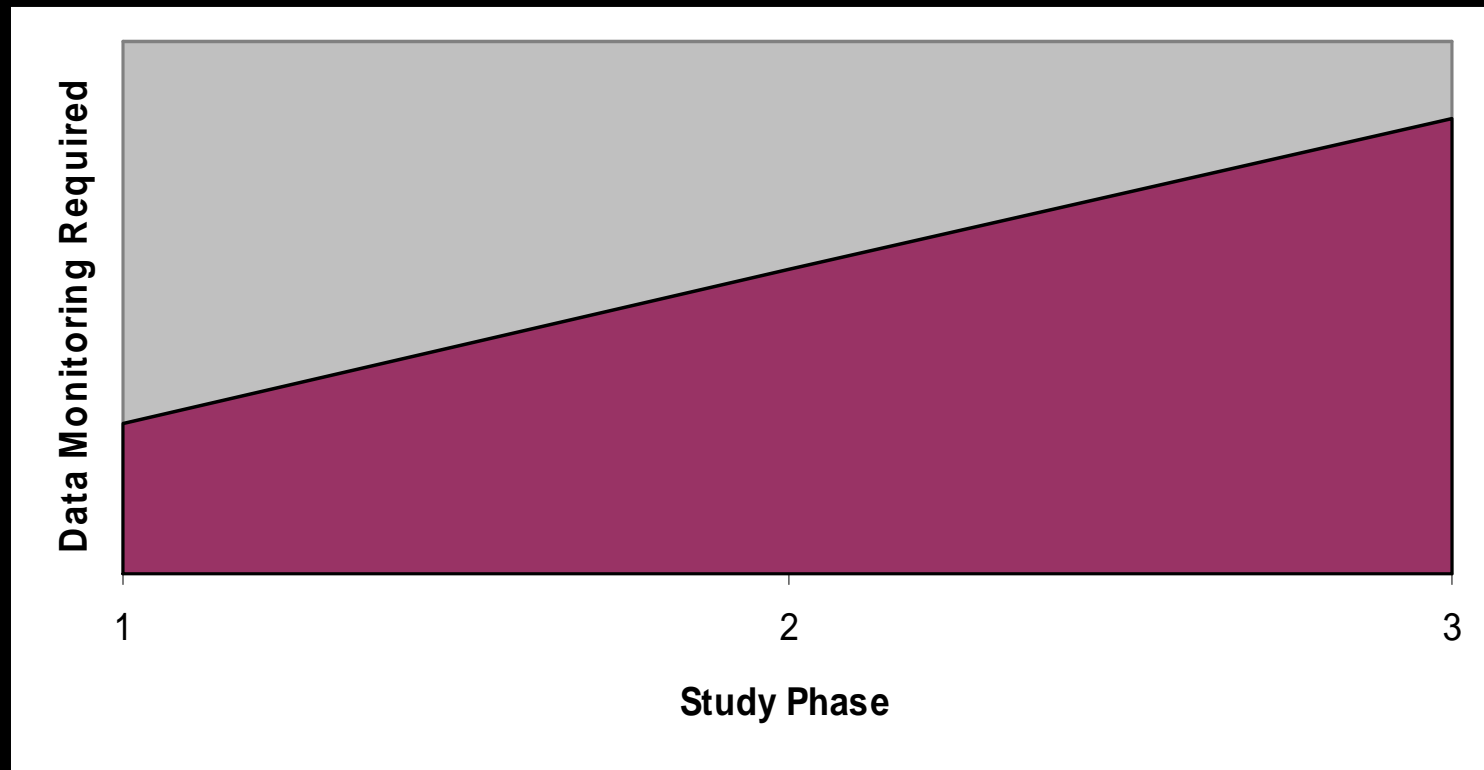
NIH Guidances/Policies for Consideration

- NICHD
- NIAAMS
- NEI
- * NHLBI *
- NCI
- NCCAM
- NIAAA
- NIDA
- GCRC

NIH

- The method and degree of monitoring should be commensurate with the degree of risk involved in participation in the trial as well as the size and complexity of the clinical trial

Sliding Scale Requirements



NIH

- All Phase III trials supported by NIH must be monitored by a DSMB
- Phase I and II studies may also use DSMBs however, smaller clinical trials may not require this level of oversight and alternative monitoring plans may be more appropriate.

NIH

- Alternative monitoring plans must have written policies and procedures which include:
 - A description of how AEs will be reported to the IRB, FDA, NIH, and OBA (if required)

NIH

- It may also include procedures for ensuring:
 - Safety of participants/volunteers
 - Validity and integrity of the data
 - Enrollment rate relative to expectation, characteristics of participants
 - Retention of participants, adherence to protocol
 - Data completeness

NIH

- Options for monitors include:
 - DSMB
 - IRB
 - Independent individual
 - Designated medical monitor
 - Principal Investigator
 - Other (e.g. Internal Committee or Board with explicit guidelines)

FDA

- Requires that the sponsor have a plan for providing Data Safety Monitoring.

FDA

- Guidance released 03/06
- Determining the need
 - Risk to Trial Participants
 - Practicality of Review
 - Assurance of Scientific Validity

FDA

- Composition of the Committee
 - At least 3 members
 - Biostatistician
 - Scientists
 - Useful Additions
 - Lay Member (individual with perspective of the studies population)
 - Ethicist
 - Without Conflict of Interest (unaffiliated is best)

FDA

- Conduct of the Meeting
 - Open section – which present data in aggregate; data from this portion may be shared with the sponsor, investigators, IRB, and other interested parties
 - Closed section – in which comparative outcome data are presented; data is confidential

FDA

- Should have written SOPs
 - Meeting schedule and format
 - Format for presentation of data
 - Specifics of who will have access to interim data and who may attend all or part of the DMC meetings
 - Assessing Conflict of Interest
 - Method and Timing of Providing Interim Reports to the DMC
- Maintain Meeting Records

FDA

- The study should be monitored for:
 - Effectiveness
 - Safety
 - Study Conduct
 - Consideration of External Data
 - Studies of Less Serious Outcomes
(different monitoring is required)

NIH/OHRP

- Information on adverse events, interim findings, and any recent literature that may be relevant to the research may not be readily available to local investigators participating in multicenter clinical trials or to their local IRBs.
- Such trials are often subject to oversight by a DSMB whose responsibilities include review of such data.

NIH/OHRP

- In such circumstances, IRBs conducting continuing review of research may rely on a current statement from the DSMB indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature relevant to the research.
- The IRB must still receive/review local, on-site unanticipated problems involving risks to subjects.

NIH/OHRP

- DSMB Summary report should document that a review of data and outcomes across all centers took place on a given date. It should summarize the DSMB's review of the cumulative toxicities reported from all participating sites, and it should also inform investigators of the study the DSMB's conclusion with respect to progress or need for modification of the protocol.
- The local investigator is required to transmit the report to the local IRB.

Data Safety Monitoring
Plan (DSMP)

VS

Quality Control (QC)

VS

Quality Assurance (QA)

Quality Assurance / Monitoring

- The FDA issued a guidance in January 1998
- Requested as part of the 3/6/00 letters to holders of gene therapy INDs
- Commonly noted as a deficiency on FDA warning letters
- QA Plan required by NIH for some applications
- Monitoring required by FDA and ICH for sponsors of multi-site studies
- Recent developments indicate that more guidance from the FDA will be forthcoming

Quality Assurance

- “All actions taken to ensure that standards and procedures are adhered to and that ... services meet performance requirements. The planned systematic activities necessary to ensure that a ...system conforms to established ... requirements. The policy, procedures and systematic actions established in an enterprise for the purpose of providing and maintaining a specified degree of confidence in data integrity and accuracy throughout the lifecycle of the data which includes input, update, manipulation, and output.”

Quality Assurance/Monitoring

- Is retrospective
- QA:
 - Ensures that SOPs for protocol development, conduct of clinical trials, and data collection/management are accurately defined and being followed
 - Reviews regulatory documents including investigational agent accountability, investigator CVs and laboratory certifications
 - Reviews selected patient charts for crucial data elements

Quality Control

- Excerpt from FDA letter (Winter 2003):
 - “The conduct monitoring plan for your clinical trial contains several deficiencies. The request extent of study conduct monitoring is described in the FDA Gene Therapy letter of March 6, 2000...Please be aware that monitoring is the process of continuous “real-time” corroboration of completeness and accuracy of information and adherence to standard procedures. We note that your descriptions ...refer to study “auditing” a retrospective monitoring...”

Quality Control

- A management function whereby control of the quality of ... components ... services ... management, production, and inspection processes is exercised for the purpose of preventing undetected production of defective material or the rendering of faulty services”

Quality Control

- Is Prospective
- The QC Program:
 - Evaluates the conduct of clinical trials and the compliance of clinical research operations staff with all federal regulations, International Conference on Harmonization Good Clinical Practices (ICH GCP) and institutional standard operating procedures (SOP).
 - Provides training to new clinical research operations personnel and continuing education to all clinical research personnel.
 - Implements or improves the operational processes established in the SOPs.

Questions?

