St. Jude Children's Research Hospital
Cancer Center

Institutional Data and Safety Monitoring Plan

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Data and Safety Monitoring Plan

The institution's data and safety monitoring plan is intended to ensure the safety of participants in clinical trials and the validity and integrity of data and reporting for all NIH-supported clinical trials. All clinical trials require monitoring commensurate with the degree of risk involved in participation as well as the size and complexity of the study. Monitoring is an ongoing process, responsibilities for which are assumed by the principal investigator and the clinical trials infrastructure of the Cancer Center. In specific settings, the final monitoring responsibilities are assigned to the St. Jude *Data and Safety Monitoring Board (DSMB)* or contracted to a *contract research organization (CRO)*. The institution's Data and Safety Monitoring Plan outlines the general process for data and safety monitoring, including institutional oversight and review procedures important to assure and document compliance. The Plan has been developed to comply with NIH/NCI guidelines published as *NIH Policy for Data and Safety Monitoring* of June 10, 1998, *Policy of the NCI for Data and Safety Monitoring of Clinical Trials* of June 22, 1999, *Further Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials* from NIH on June 5, 2000, and *Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by the NCI* of April, 2001. Many of the elements of protocol development and review, policies regarding protocol approval, safety procedures and reporting, investigator education, and institutional administrative oversight are included in the *Clinical Investigators Handbook*, relevant details of which are summarized in the current document. Requirements for adverse event reporting are abstracted in Appendix 1.

1. Monitoring the Progress of Trials and the Safety of Participants

Monitoring for clinical trials is a continuous, ongoing review of the conduct of the trial, including adherence to study design and documentation of appropriate reporting of related toxicities. The responsibilities for monitoring are shared amongst the *Principal Investigator (PI)* and the *Vice President for Clinical Trials (VPCT)* through the *Central Protocol and Data Monitoring Office (CPDMO)*. Auditing is a *post facto* review that regularly assesses major aspects of the trial, including compliance with the study design, documentation required for primary study objectives, toxicity reporting, and data integrity. Auditing is conducted under the supervision of the VPCT. The Clinical Protocol Scientific Review and Monitoring Committee's Monitoring Subcommittee and the institution's external DSMB have responsibility for evaluating study conduct during the course of a trial based upon data provided by the Principal Investigator, the CPDMO, and other components of the Center's clinical trials infrastructure.

I.A Institutional Oversight of Clinical Trials Monitoring

All protocols include a section outlining the data and safety monitoring plan (DSMP) for that study. The *Clinical Protocol Scientific Review and Monitoring Committee (CPSRMC)* reviews the proposed data and safety monitoring plan, approval of which is required prior to opening a study for patient accrual; the DSMP is also a component of the protocol as reviewed by the *Institutional Review Board (IRB)*.

The CPSRMC was initiated in 1995 to review the science of all proposed Cancer Center studies and includes faculty who are clinical investigators, translational and basic laboratory scientists, and biostatisticians as well as non-faculty professional staff. The Committee meets every two weeks and reviews concepts and protocols proposed by institutional investigators, both those originating within the Center and those for which St. Jude will be a participant in a multi-institutional or cooperative group trial. The review addresses the scientific basis of the study, likelihood of achieving the primary and secondary objectives, and the study design. The Committee must approve the DSMP of each protocol. The Committee regularly reviews prioritization schemes submitted by each Cancer Center Program. The impact of new studies on the approved Program

prioritization scheme is assessed. CPSRMC approval is required for institutional studies before submission to the IRB; for cooperative group trials, CPSRMC approval must be documented before the study can be opened for accrual at SJCRH. Annual CPSRMC reviews focus on the scientific progress of the trial, accrual, and the ability to achieve the protocol objectives; reports of the Monitoring Subcommittee are reviewed as a part of the annual review process.

Effective 2001, the *Monitoring Subcommittee of the CPSRMC (MS/CPSRMC)* is responsible for protocol monitoring on an ongoing basis to ensure that the rights and well-being of the patients/subjects are protected, that patients are treated in full compliance within the parameters outlined in the protocol, that adverse event and serious adverse event reports have been completed and appropriately submitted according to institutional and regulatory policies and procedures (Appendix 1), and that the data regarding all primary objectives of the study is accurate and complete. Monitoring and auditing reports are submitted to the MS/CPSRMC according to specifics outlined below or as indicated in the protocol DSMP. The MS/CPSRMC summarizes the results of ongoing monitoring, regular auditing, and current protocol status in reports to accompany annual protocol reviews considered by the CPSRMC; summaries are also attached to continuing reviews submitted to the IRB. The Monitoring Subcommittee is chaired by the Monitoring Vice Chair of the CPSRMC, in addition including 3 faculty involved in clinical investigation and 2 research nurses; the CPDMO is represented by the director and staff involved in monitoring.

The CPSRMC reports through its chair to the Cancer Center Director, with a direct line, as well, to the VPCT. The director of the CPDMO also reports directly to the VPCT. The organization of the clinical trials infrastructure in support of clinical investigation, monitoring, and regulatory oversight is depicted in Appendix 2.

Review by the CPSRMC and the IRB assure thorough consideration of the study DSMP. New studies are assigned to the MS/CPSRMC for monitoring as the trial is implemented, based upon documentation by the CPDMO that approvals by the IRB, CPSRMC, and any relevant sponsors and/or regulatory agencies have been confirmed, and that required data capture forms have been developed. The VPCT confirms that the trial's PI and co-investigators have been certified in the conduct of clinical research.

I.B Responsibilities for Monitoring Clinical Trials

B.1 For all protocols *except* those (1) related to a drug or device for which SJCRH holds the IND or IDE, or (2) sponsored by a pharmaceutical company, the primary responsibility for monitoring is shared between the respective Program (represented by the principal investigator and an assigned research nurse (RRN)) and the CPDMO. The PI and RRN are responsible for continuously monitoring the conduct of the trial and are the primary individuals charged with identification and reporting of all AE and SAE occurrences; should there be differences in coding or attribution between the RRN and the PI, the issues will be presented immediately to the Vice President for Clinical Trials whose decision will be final.

Monitoring is conducted by the CPDMO. The CPDMO provides systematic monitoring for all studies for the following ***central elements***: *protocol eligibility* (direct source documentation of eligibility as defined in the protocol), *appropriateness of consent documentation*, and *timeliness and accuracy of data, including the timeliness of reporting adverse events and serious adverse events*. Confirmation of patient eligibility is reported directly to the PI and the primary attending physician. Monitoring for ***study conduct*** includes but is not limited to

all elements identified in a modified version of the *Clinical Data Update System* (CDUS, Appendix 3). Monitoring for central elements will be performed on all patients; typically, monitoring for study conduct (CDUS elements) will be performed on the first two patients for every trial or as indicated (section IV). Reports documenting the central elements are generated at monthly or quarterly intervals depending upon the study type and potential risks (see section IV.A-D,F) or as specified in the DSMP. Other monitoring reports are generated at protocol specified intervals (see section IVA-D,F). CPDMO monitoring reports are reviewed by the PI and the RRN; reports and documentation of any corrective actions that might be required are forwarded to the MS/CPSRMC and the VPCT at specified intervals.

B.2 For clinical trials for which SJCRH holds the IND or IDE, the primary responsibility for monitoring is assigned to the CPDMO or an outside *contract research organization (CRO)*. Responsibilities of monitoring are shared with the PI and the RRN re ongoing identification of toxicities and appropriate reporting, but the level of direct oversight and the intensity of monitoring is assumed by the CPDMO or the CRO according to the specifics of the DSMP incorporated in the protocol document.

B.3 For clinical trials sponsored by a pharmaceutical company, monitoring will be defined by the company which holds the IND and summarized in the DSMP included in the protocol document.

II. Assuring Compliance with Requirements for Reporting Adverse Events

All adverse event (AE) and serious adverse event (SAE) forms are submitted by the PI directly to the IRB and the Office of Regulatory Affairs (ORA), as summarized in the *Clinical Investigators Handbook* outlined in Appendix 1. The ORA is responsible for submitting AE and SAE reports as required to study sponsors or regulatory agencies, including the FDA (for FDA regulated agents or devices) and the NIH Office of Biotechnology Activities (for gene transfer trials). The ORA also confirms to the PI that necessary communication has been effected and documented to the regulatory agencies. The MS/CPSRMC and VPCT review summaries of all AE and SAE reports and of all ORA actions related to AE and SAE reporting; any discrepancies are summarized in regular reports reviewed by the Director of St. Jude. The director of the ORA reports jointly to the Vice President for Clinical Trials and the Vice President for Therapeutics Production Quality.

III. Notification of NCI Regarding Temporary or Permanent Suspension of a Funded Clinical Trial

The CPDMO is responsible for notifying all clinical investigators, the *Research Administration Office (RAO)*, and the ORA whenever accrual to a clinical trial is suspended or terminated. When accrual is suspended or terminated for reasons outside the planned study design (e.g., unanticipated toxicities, inadequacies in protocol compliance or conduct resulting in suspension by the CPSRMC or the IRB) or when administrative reasons require suspension for an estimated duration in excess of one month, the RAO notifies the Grants Management Officer of the NCI and all NCI program directors responsible for grants related to the affected trial. The ORA is responsible for notifying the study sponsor and regulatory agencies as may be required.

IV. Assigning Monitoring Levels for Protocol Compliance – Elements of Monitoring and Reporting

Trials are monitored according to the type of trial and potential risks, modified according to whether the institution holds the IND or IDE associated with the trial. For all studies when NCI holds the IND or IDE, monitoring will be conducted according to the guidelines for institutional studies.

IV.A ***For non-therapeutic trials and those trials without significant health or safety risks*** (e.g., trials based upon survey research, questionnaires, blood or tissue sampling, observational studies, or limited interventional studies typically addressing research in cancer prevention and control), monitoring is primarily through the principal investigator and research nurse (RRN). The CPDMO monitors all central elements on an annual basis. The conduct of the study and any observed toxicities (including AE and SAE events) are reported in annual documentation to the MS/CPSRMC.

IV.B. ***For institutional phase I studies*** (i.e., trials that evaluate new therapeutic interventions, including determining a safe and tolerated dose or regimen, alternatively evaluating the feasibility of medical devices or procedures, and including evaluation of toxicities and potential adverse events; trials may include correlative pharmacologic or biologic studies), the CPDMO monitors central elements continuously; in addition, for dose-escalating trials, the CPDMO continuously monitors the number of patients at each respective dose level and the required toxicity evaluation intervals to assure the conduct of the trial complies with protocol design. Study conduct (CDUS elements) and timeliness and accuracy of data will be monitored regularly for the first 3 patients of the trial (and reported to the PI no later than at the time the third consecutive patient completes course 1) and for one patient per dose level. The PI and CPDMO submit reports to the MS/CPSRMC at least quarterly, or as required in the protocol DSMP.

IV.C ***For institutional phase II studies*** (i.e., trials that determine the efficacy of an agent, regimen, procedure, or device, often including pharmacologic or biologic correlations), the CPDMO monitors eligibility and consent documentation and other central elements continuously. The timeliness and accuracy of data, study conduct elements, and response evaluations (to include source documentation of coded responses according to protocol design) will be monitored regularly for the first 2 patients of the study (and reported to the PI no later than at the time the third consecutive patient completes response evaluation) and for one or more patient(s) per year, estimated to equal at least 10% of total patients accrued. The PI and CPDMO submit reports to the MS/CPSRMC at least every 6 months, or as required in the protocol DSMP.

IV.D ***For institutional phase III studies*** (i.e., studies with survival or disease control as an endpoint, or those with comparative treatment regimens; see Section V.1), the CPDMO monitors eligibility and consent documentation monthly and other central elements continuously; in addition, the timeliness and accuracy of data, study conduct elements, and response evaluations (when indicated and to include source documentation of coded responses according to protocol design) will be monitored regularly for the first 2 patients of the study (and reported to the PI no later than at the time the third consecutive patient completes response evaluation or 6 mos. on study) and for one or more patient per year, estimated to equal at least 10% of total patients accrued. . Other protocol endpoints listed as primary objectives (e.g., survival, event-free survival, specific toxicities or quality of life measures) are monitored on an annual basis. The PI and CPDMO submit reports to the MS/CPSRMC at least every 6 months, or as required in the DSMP. All phase III trials (as defined in Section V.1) are monitored by the SJCRH external Data and Safety Monitoring Board (see Section V).

IV.E ***Protocols for which the institution holds the IND or IDE*** require more frequent source documentation regarding validation of database entry and capture/reporting of adverse

and serious adverse events, including confirmation that required reports are submitted to the IRB and all sponsoring organizations or agencies; in addition, the integrity of the study with respect to approvals for modifications and documentation of deviations/violations will be monitored. The enhanced level of ongoing institutional monitoring required when SJCRH holds the IND or IDE is based upon the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice and is assigned to the CPDMO (see Appendix 4, *Standard Operating Procedures for CPDMO Clinical Trial Monitoring: St. Jude Sponsored IND or IDE; issue date 7/02/01*) or through contract with an outside contract research organization (CRO). The respective responsibilities of the PI, the CPDMO, and the CRO (when utilized) are to be defined in the DSMP, along with the identified Operating Procedures (when monitored by the CPDMO) or customized monitoring plan (when monitored by an outside CRO). Monitoring reports are submitted to the MS/CPSRMC at intervals dependent upon study type (see Sections IV.B-IV.D), or as required by the DSMP.

IV.F Multi-site studies

IV.F.1 Protocols ***sponsored by an NIH-supported cooperative group*** or consortium are monitored according to the procedures specified for that group.

IV.F.2 ***Independent studies in which the institution is a participant*** require a summary of the DSMP for the collaborative trial; the CPSRMC will review the DSMP as a part of the initial review process in parallel with review by the IRB. Monitoring at St. Jude will be according to the requirements for an institutional study of comparable type, including reporting for AEs and SAEs according to institutional standards and through the appropriate channels as other institutions may hold the IND or IDE relevant to the trial.

IV.F.3 For ***trials centered at or led by St. Jude clinical investigators***, monitoring requirements are identical to those noted above for the appropriate phase of the trial. Each collaborating institution is responsible for summarizing its monitoring plan for review by the MS/CPSRMC at the time the trial is initiated. The SJCRH CPDMO will be responsible for monitoring the trial within 6 months of the first protocol entry or at point triggered by the study type. Subsequent monitoring will be by the participating institution when the respective monitoring plan has been approved by the SJCRH Monitoring Subcommittee; when not so approved, SJCRH will be responsible for monitoring at annual intervals or as appropriately documented in the protocol document. Reports of the study monitoring directly related to St. Jude participation are submitted to the MS/CPSRMC as required by the study type; reports including all collaborating institutions are submitted annually to the SJCRH MS/CPSRMC.

IV.G ***Protocols sponsored by a pharmaceutical company*** are monitored by the company holding the IND; specific arrangements for monitoring are included in the institutional agreement with the sponsoring company and outlined in the DSMP described in the protocol. Monitoring reports are submitted to the VPCT by the company.

V. Monitoring by the St. Jude external Data and Safety Monitoring Board

The St. Jude external DSMB includes nationally recognized clinical investigators and a biostatistician conversant with pediatric oncology; the chair is Jeannette Pullen, MD, Director of Pediatric Hematology/Oncology, University of Mississippi School of Medicine. The Board includes representatives from the institution, as well as patient/parent advocates. The Board held its initial meeting at St. Jude 15 December, 2000, and convenes every 6 months to review

materials for a sizable percentage of institutional trials so identified. The Department of Biostatistics prepares reports for the Board based upon guidelines outlined in the DSMB charter and as requested by the Board. The validity of the data is based upon the clinical trials infrastructure and the requirements for primary monitoring by the PI, RRN, and CPDMO as summarized above. Reports of the DSMB are submitted independently to the Director, subsequently forwarded to the IRB, with a copy to the principal investigator and the Vice President for Clinical Trials.

V.1 protocols originating within the St. Jude Cancer Center are monitored by the ***institution's DSMB*** in the following categories:

V.1.a all phase III trials, defined as randomized trials and all trials *with survival or disease control comparison as an endpoint*;

V.1.b any study referred to the DSMB by the principal investigator, Program leader, or the IRB, or

V.1.c studies that incur unique or potentially significant risks, to include all gene therapy protocols and all upfront therapeutic window protocols.

VI. Assuring Data Accuracy and Protocol Compliance

VI.A Data Integrity – Auditing

VI.A.1 All Cancer Center protocols will be audited on a scheduled basis beginning in the first half of 2003. Auditing is performed at the closure of studies listed as ***non-therapeutic or without significant risk***. In such instances, auditing includes a random check of study conduct, data completeness and accuracy based upon a minimum of 3 cases per trial or 10% of all cases accrued. For all investigator-initiated ***therapeutic trials***, auditing is performed on an annual basis, reviewing a minimum of 4 cases/year or those appropriate to result in an ultimate audit of 20% of cases based upon projected accrual and rate of entry, whichever is larger. When SJCRH holds the IND or IDE, the number of cases audited per year is increased to review 25% of projected cases; any deficiencies detected in the auditing process typically require auditing of 50-100% of cases dependent upon the seriousness of such deficiencies and determined by the VPCT. All studies are audited upon completion. St. Jude Domestic Affiliate institutions participate in clinical investigation but do not share responsibilities for study design or conduct comparable to a multi-site collaboration; protocol data is audited on an annual basis for each Affiliate institution.

VI.A.2 For studies ***sponsored by a pharmaceutical company or centered at another institution***, auditing will be conducted by the responsible outside party along lines identified in the DSMP.

VI.A.3 For ***multi-site collaborative trials where St. Jude is the coordinating institution***, the VPCT office will arrange to audit each collaborating institution 12 months after the first monitoring visit at the collaborating center. Auditing will be repeated at the completion of the study as required in the protocol DSMP.

VI.B Elements of Auditing

VI.B.1 Each audit will consist of review and evaluation of: 1) compliance with IRB requirements; 2) conformance with informed consent requirements; 3) the pharmacy and completion of NCI Drug Accountability Forms (DARFs) or drug logs; and 4) individual patient cases. All data that impact on the interpretation of primary study endpoints will be verified with source documents for the selected sample. Investigator compliance with the protocol also will be evaluated for the cases selected.

Appendix 1. Reporting Requirements for Adverse Events

(abstracted from SJCRH Clinical Investigator's Handbook, approved 10/18/2000.

Reporting Adverse Events, Deaths and Higher than Expected Aggregate Toxicities

Principal Investigators are responsible for reporting to the IRB any unexpected adverse events that impact the safety of, or risk to their subjects. These reports should be completed in a timely fashion. If an unexpected death occurs, a verbal report should be provided to the IRB office immediately and followed by a written report within 48 hours. Serious, unexpected events are to be reported within 10 working days. At the same time, the investigator will notify the study sponsor (NIH or pharmaceutical company), Cooperative Group, the FDA, or other agencies as appropriate. In the future, the Regulatory Affairs Office will assist investigators in notifying external sponsors or agencies.[1] The Principal Investigator is responsible for reviewing the aggregate toxicity reports for his/her protocols at six month intervals and reporting to the IRB if the frequency of serious toxicities exceed those expected as defined in the protocol or based on clinical experience or the published literature.

Any proposed changes in the consent form or research procedures resulting from the report are to be prepared/identified by the Principal Investigator and submitted with the report and an amendment form to the IRB for approval.

The following definitions apply:

- A **serious event** refers to any event in which the outcome is fatal or life-threatening, causes permanent disability or incapacity, or is a congenital anomaly, cancer, or overdose, that causes or prolongs inpatient hospitalization.

- An **unexpected adverse event** refers to those not identified in their specificity or severity in the current risk documents (e.g., investigator's brochure) or through clinical practice.

The following are considered reportable:

Any injuries, serious event or other unexpected adverse events involving risk to subjects or others which occur at a frequency above that considered acceptable by the investigators or the IRB.

The IRB Chair will review the report and bring it to the next IRB meeting.

Based on the frequency and seriousness of adverse events, the IRB may deem it necessary to temporarily or permanently suspend accrual or terminate a research study or studies. The IRB will engage the investigator in making such a decision.

<u>Adverse Event Reporting Requirements for Investigational Agents Sponsored by NCI</u>

Adverse event collection and reporting is a routine part of every clinical trial. The first step is to identify the event using the Common Toxicity Criteria (CTC). The severity of the event should then be graded using the CTC. Next, determine if the adverse event is related to the medical treatment or procedure (attribution). If so, determine whether the adverse event is expected or unexpected. With this information and the adverse event reporting section in each protocol, the investigator can determine whether an adverse event should be reported to the NCI as an expedited report (AdEERS) or a routine report (CDUS or CTMS).

1. Reporting requirements and timing of reporting are dependent on the Phase of trial, grade, attribution and whether the event is expected or unexpected as determine by the NCI Agent

Specific Expected Adverse Event List, protocol and/or Investigator's Brochure. An expedited adverse event report requires submission to CTEP via AdEERS or the *Adverse Event Expedited Report - Single Agent* or *Multiple Agents*) paper templates available on the CTEP Home Page, http://ctep.info.nih.gov). Reports should be submitted within the timeframes specified below. All expedited adverse event reports should also be sent to the local Institutional Review Board (IRB). Routine expected adverse events are normally reported in the annual report to the IRB.

2. Attribution - An expedited report is required for all unexpected and expected Grade 4 and Grade 5 adverse events regardless of attribution for any Phase of trial (1, 2, 3). An expedited report is required for unexpected Grade 2 and Grade 3 adverse events 3ith an attribution of possible, probably or definite for any Phase of trial (1, 2, 3). An expedited report is not required for unexpected or expected Grade 1 adverse events for any Phase of trial (1, 2, 3).

3. Expedited reports of the *Adverse Event Expedited Report – Single Agent* or *Multiple Agents* paper templates are to be sent to – Investigational Drug Branch (IDB), PO Box 30012, Bethesda, MD 20824 or by fax to (301) 230-0159.

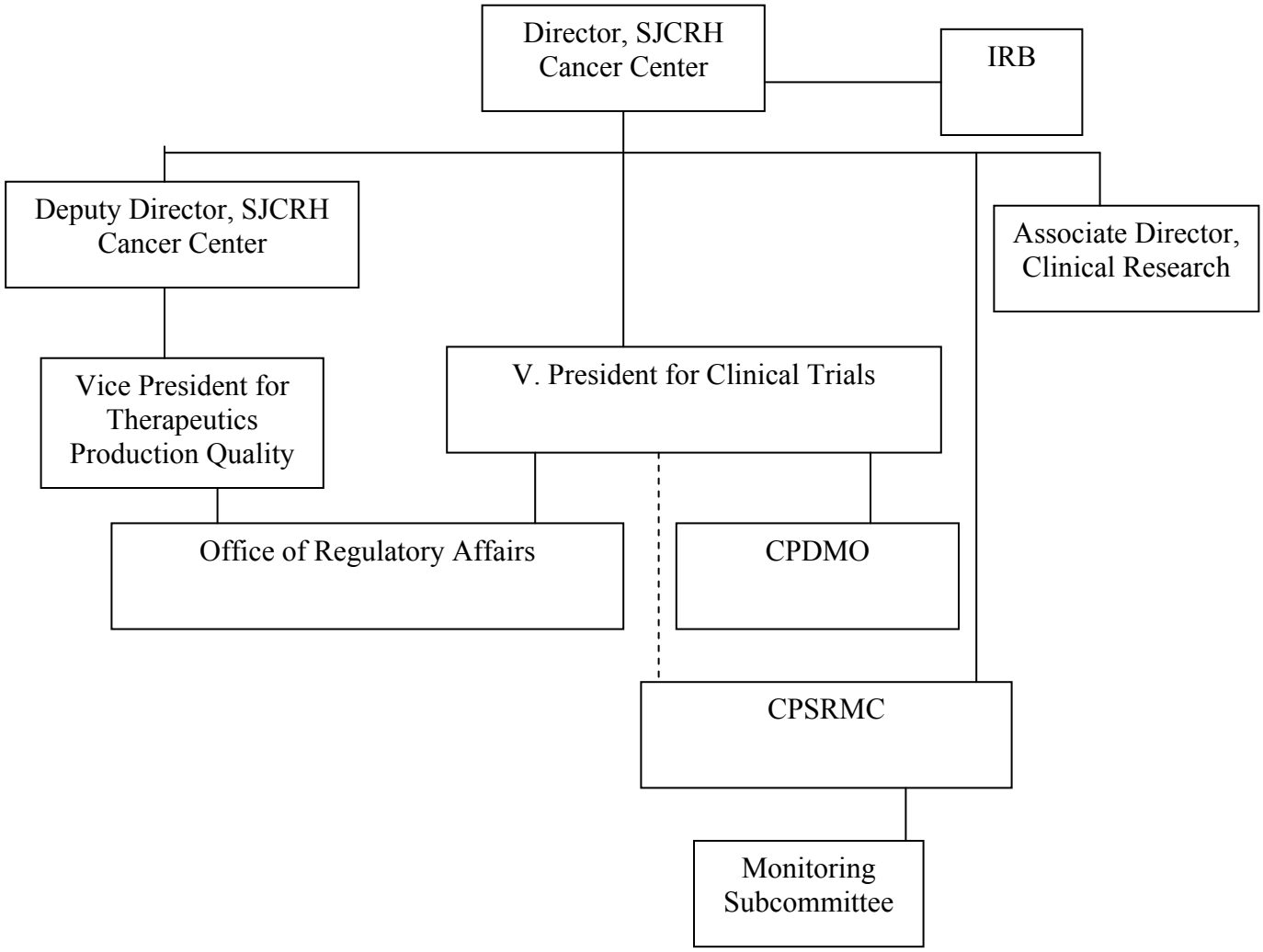
4. Telephone reports to the IDB at (301) 230-2330 (available 24 hours a day – recorder after hours 5 pm to 9 am EST).

5. After January 1, 2001, all expedited reports must be submitted using the new AdEERS web application or the *Adverse Event Expedited Report – Single Agent* or *Multiple Agents* paper templates. The AdEERS standard is implemented for all trials regardless of dates of review and approval. Expedited reports submitted using any of the previous adverse event forms will not be acceptable. Assistance for using AdEERS or for completion of the AdEERS templates is available at http://ctep.info.nih.gov.

6. Expedited reporting may not be appropriate for certain protocols where an adverse event is expected. The exception or acceptable reporting procedures must be specified in the text of the approved protocol. Therefore, the protocol guidelines would supersede the standard guidelines for adverse event reporting.

[1] Reporting will be modified effective 1 October, 2001, in accordance with the institutional DSMP. The PI will forward AE and SAE forms to the IRB and the Office of Regulatory Affairs (ORA). The ORA is responsible for reporting directly to the study sponsor or regulatory agencies as appropriate (see Section II. of DSMP).

Appendix 2.
Organization of Clinical Trial Infrastructure for Monitoring Clinical Trials



CPDMO = Central Protocol and Data Monitoring Office
IRB = Institutional Review Board

Appendix 3.
Monitoring Elements as summarized in the NCI *Clinical Data Update System (CDUS)*

Patient-Specific Data

- demographics
- date of entry
- treatment status (receiving therapy)
- off-therapy reason(s)
- subgroup on protocol
  - eligibility
  - performance status
  - prior therapy
  - disease code (diagnosis, SNOMED)
- treatment by course
  - course ID
  - start date
  - rx assignment (ph I)
  - BSA or weight
- dose of agent
  - agent
  - dose modification
  - total dose/course
- adverse event reporting
  - type
  - grade
  - attribution
  - reporting
- response
  - evaluable
  - best response at time of evaluation

Appendix 4.
Central Protocol and Monitoring Office: Standard Operating Procedures, *St. Jude Sponsored IND or IDE*