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Good Clinical Practice and the Conduct of Clinical Studies in Pediatric Oncology

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Introduction

Good clinical practice (GCP) is an international ethical and scientific quality standard for trials involving human subjects. The many activities covered by GCP include trial design, definition of scientifically and ethically sound trial objectives, oversight of trial activities, data collection and quality assurance, study analysis, and human subject protections. All of these activities are intended to support clinical research, with the ultimate goals of improving the health and welfare of patients and advancing biomedical science. GCP is fundamentally a system in which responsibilities are shared by clinical investigators, institutions, institutional review boards, industry sponsors and government regulators. One of the great challenges in applying good clinical practices is defining the roles and responsibilities of those involved and ensuring a dynamic process in which contributions are complementary. Here we will discuss the principles that guide good clinical practice standards, with particular emphasis on how they to relate to pediatric oncology research and recent efforts at harmonization. We will also review the clinical trials process and the roles of the participants, highlighting the pivotal role of the clinical investigator and the research team. Finally, we will briefly review the historical aspects of drug development regulations in the United States and the current regulatory paths for pediatric oncology drug development. Where relevant, we describe historical events that underlie many of the regulations and their current applications, and provide practical examples.

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I. Overview of Good Clinical Practice and International Harmonization

GCP is a roadmap of responsibilities that ensures that clinical research involving human subjects is consistent with appropriate laws, regulations and ethical principles [1-3]. Compliance with the principles of GCP provides assurance that the rights, confidentiality, and well-being of subjects are protected and that the clinical trial data and reported results are credible. These principles were collaboratively developed by the United States, European Union, and Japan over the past 25 years through the International Conference on Harmonization (ICH), established to develop and harmonize technical requirements for drug development [4]. Working groups composed of subject matter experts representing the three regions' regulatory agencies and pharmaceutical manufacturers convene several times a year to develop guidance that reflects the collective current wisdom about how best to develop and test medicinal products. ICH documents also address a broad array of product testing issues, including manufacturing, non-clinical, and clinical safety and efficacy evaluation issues. The ICH process is fluid; new working groups are formed as needed, and older documents are updated as new issues arise. For example, an expert working group recently completed guidance on assessment of drugs that have the potential to prolong the QT interval. A list of key ICH documents and their focus is presented in Table 1. Table 2 lists U.S. Federal Drug Administration (FDA) regulations related to good clinical practice and clinical trials.

II. Conducting Clinical Trials

Evidence-based medicine is the standard of care for treatment of disease. Through clinical research we expand on that knowledge to improve evidence-based standards. In the United States, clinical trials have been a standard approach to the care of children with cancer since the 1960s. Because childhood cancer is rare, advances in therapy depend on collaborative clinical trials conducted by cooperative groups and consortia [5,6]. There have been a number of pediatric cooperative groups in the U.S., beginning with the Southwest Oncology Group (SWOG) in the 1960s and 70s, followed by the Children's Cancer Group (CCG), the Pediatric Oncology Group (POG), the National Wilms Tumor Study Group, the Intergroup Rhabdomyosarcoma Study Group (IRSG), and more recently, the Children's Oncology Group (COG). COG is presently a National Cancer Institute (NCI)-funded international multi-center clinical trials organization headquartered in the U.S. with more than 200 sites in North America, Australia, the Netherlands, and Switzerland. It brings together specialized professionals to conduct focused clinical investigations in children with cancer.

While clinical trials have become a standard approach to cancer treatment and have improved pediatric cancer outcomes, clinical research introduces additional risk(s) that must be balanced with potential benefit(s) [6]. Consider, for example, a randomized trial in which a subject is assigned to a treatment arm that ultimately is shown to be less effective, or equally effective but with more severe toxicity. It is imperative that clinical researchers follow GCP to ensure the safety of the clinical trial subjects as well as the integrity of the data, which will be used to support changes in evidence-based care and the regulatory approval of new medicines.

Role of the Sponsor(s)—GCP defines the sponsor as “an individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of clinical research.” Sponsors oversee the Investigational New Drug (IND) application and are ultimately responsible for the research and for ensuring the compliance of the investigators. Sponsors must provide investigators with adequate information to support the use of a test product. Sponsors create and update the Investigators Brochure (IB), a document compiling relevant preclinical and clinical information about a new drug, or a new indication for a known drug. It is not unusual in pediatric cancer investigations to have an IND application for the new pediatric use of a commercially available drug. It is the sponsor who ultimately submits a marketing application to the regulatory authorities.

The sponsor is responsible for quality assurance and quality control of the studies. Standard operating procedures (SOPs) define duties to ensure compliance with the protocol at each stage of the trial. The sponsor ensures statistical analyses of the study and where necessary designates an independent data monitoring committee [7]. For example, COG has a Data Safety Monitoring Committee that meets semi-annually (more often if necessary) to ensure that study monitoring plans are followed.

The sponsor is responsible for maintaining essential documents, including the IB, protocol, agreements, regulatory documents, case report forms and the records of investigational product accountability. The sponsor also determines subject and investigator compensation and trial financing.

While many of the sponsor's obligations can be delegated to a clinical research organization (CRO), the sponsor is ultimately responsible for the IND. In pediatric cancer, sponsors include the Cancer Therapy Evaluation Program of the NCI, the pharmaceutical industry, and in some cases individual investigators or institutions (known as sponsor investigators). Regardless of the sponsor or the funding mechanism, GCP must be followed. Where trials cross international boundaries, additional local sponsor requirements may be necessary. Health Canada, for example, requires that a Canadian Senior Medical Officer be appointed as the Canadian sponsor of all COG studies in that country.

In the cooperative group setting, a physician is designated as the Study Chair of each therapeutic clinical trial to ensure sponsor-required medical expertise. The multidisciplinary study committee (pediatric oncologists, biostatisticians, pharmacologists, surgeons, pathologists, radiation oncologists, radiologists, nurses and clinical research associates) also collectively ensure quality design. Further, an independent multidisciplinary Protocol Review Committee reviews the scientific merit and other aspects of each COG therapeutic study before final submission. COG in part manages its sponsor obligations through its Statistics and Data Center.

Role of the Investigator—The investigator—the physician responsible for conduct of the clinical trial at the local site—is expected to be aware of and compliant with GCP and regulatory requirements and with the protocol and its eligibility, testing requirements, treatment plan, therapy modifications and reporting requirements. GCP defines a sub-investigator as “any individual member of a clinical trial team designated and supervised by the investigator to perform critical trial-related procedures and/or make important trial-related decisions (e.g. associates, residents, research fellows).” Investigators must be qualified by education, training and experience.

Each investigator provides a curriculum vitae in the form of a “biosketch” to COG documenting qualifications and undergoes mandatory human subject protection training as part of the membership application process. Disciplines within COG set standards for membership that ensure adherence to specific professional practice standards. Investigators also file an FDA 1572 Statement of Investigator form annually affirming investigator responsibilities, which include an agreement to follow the protocol, conduct or supervise the study, obtain informed consent per regulations, report adverse events, understand potential risks and side effects of the test product, ensure the clinical team understand obligations, keep accurate records for inspection, keep the IRB informed, and comply with all other regulations.

The investigator is responsible for recruiting study subjects at his/her clinical site and for their welfare. The investigator must be a qualified physician, as he/she is responsible for all trial-related medical decisions and must be able to provide medical care for any adverse events. The investigator must obtain informed consent of the study participant (in the case of pediatric research subjects, parental permission and age –appropriate participant assent), collect the

protocol-specified evaluations, and report safety information to the IND sponsor. The investigator may delegate the consenting process to other appropriately qualified trial staff based on guidance from the local IRB. The investigator must also account for the investigational medical product, maintain accurate records, and provide interim reports to the Institutional Review Board (IRB). Obligations of clinical investigators are delineated in federal regulations, in the ICH GCP guideline, and within each institution where clinical research is conducted [8].

Institutional Review Board/Research Ethics Board (IRB/REB)—The Investigator submits all research to the Institutional Review Board/Research Ethics Board (IRB/REB) of record for approval before initiating any clinical research study at the local site. The submission includes the sponsor-provided protocol document, study consent forms, IB, and any other written material that will be provided to a subject (questionnaires, information packages, etc.). During each year of the study the investigator must submit at a minimum a progress report and request renewal and reapproval of the research by the IRB/REB. The IRB/REB will require an updated IB as well as a summary of progress. For example, in the COG the Study Chairs with the support of biostatisticians produce study updates based on the monitoring plan and provide them to local investigators for IRB/REB submission.

All changes (amendments) to an ongoing protocol also require approval of the IRB/REB. Of particular importance is new information that might affect a subject's desire to continue participating in a study or that might alter the risk and benefit balance of the research. Additionally, any premature terminations or trial suspensions must be brought to the attention of the local IRB/REB. The investigator is then responsible for carrying out instructions from the sponsor and the local IRB/REB regarding continuation or discontinuation of the study. The investigator must provide proof to the sponsor that appropriate IRB/REB approvals have been obtained. Many of these processes are carried out electronically. The COG, for example, has an on-line tracking system whereby dates of initial, continuing review, and amendment approvals are entered into a web-based system. The COG links subject enrollment on a given trial at the local site to this process, thus assuring that protocols meet regulatory review and approval.

Informed Consent—Prospective participants cannot be enrolled into a trial without their consent. Elements of the consent form and the consent process are set forth in federal regulations and guidance documents [9] (Table 2) Before they consent, study participants must be informed of known and potential risks of participation in the trial, even if the likelihood of risk is remote. The IRB at each participating institution or a central IRB must review and approve the consent form and the clinical research protocol before the study can be initiated at that institution. The composition and duties of the IRB are described in the ICH GCP guidelines. Investigators must ensure that the consent process is free of coercion and provide sufficient time for decision-making by the subject. Legal rights of the subject may not be waived, either verbally or in writing, and consent must be personally dated.

Mechanisms exist to strengthen human subject protections for particularly vulnerable study participants, such as children, who cannot give valid consent. The parent or legal guardian gives permission for a child to be enrolled in a research study. ICH E11 addresses some of the considerations unique to pediatric clinical trials, including ethical issues. In rare circumstances when it is not possible to obtain a participant's consent because of the nature of his or her illness or injury, and when obtaining consent from a legally acceptable representative (e.g., next of kin) is not feasible, the FDA and other Department of Health and Human Services regulations may permit the clinical trial to proceed with a waiver of consent.

Children are considered a vulnerable population, and additional safeguards are in place to protect them. The age at which a child or legal representative may give consent, and the use of an assent process for minor children, are based on local IRB/REB guidance. If a subject or legal representative is unable to read, an impartial witness must be present during the consent discussion and must sign and date the consent attesting that the information in the consent form is consistent with the discussion, that the subject appears to understand the information, and that consent was given freely.

All subjects enrolled in a clinical trial must first be fully informed about the trial, and each subject (or legal representative) must sign and date the IRB/REB-approved consent form prior to participating. If possible, the consent document should have an approval or revision date. This information assures that the correct version is being used. If the consent form is changed during a study and the changes affects subjects currently enrolled, those subjects must sign the revised version. In addition, the regulations permit the use of either a written form that embodies the required elements of informed consent (Table 3) or a "short'" form stating that the elements of informed consent have been presented orally. If a short form is used, the oral presentation must be witnessed and the IRB/REB must review and approve a written summary of the information presented.

Participants must be informed which procedures are study-related, i.e., those undertaken specifically for study purposes rather than standard-of-care procedures. Taking extra blood or bone marrow samples, as might be the case in leukemia trials, would be considered a study-related procedure requiring prospective consent.

Resources—GCP requires that an investigator have adequate resources to carry out a clinical trial. Resources include the ability to recruit sufficient numbers of research subjects, which is ascertained through careful review of inclusion and exclusion criteria. Resources on-site must also be in place. The investigator must have adequate time to carry out his/her study obligations and oversee delegated study duties. Delegation must be made to appropriately qualified staff who have sufficient time to carry out the duties and have adequate information about their specific roles. Delegation logs are used to ensure that all required procedures are undertaken by appropriate individuals.

In the COG example, each site has a Principal Investigator with ultimate responsibility, plus co-investigators from a variety of disciplines, such as pathology, surgery, radiation oncology and nursing. The site also has a research coordinator called a Clinical Research Associate (CRA) to whom many of the day-to-day tasks are delegated.

Facilities appropriate for the study must also be available. For example, if a study requires radiation therapy, the facility must have access to an approved radiation therapy facility sanctioned by the Quality Assurance Review Center (QARC). If a stem cell transplant is a study component, a FACT (Foundation for the Accreditation of Cellular Therapy)-accredited transplant facility must be available. A careful review of study procedures will reveal requirements and compliance issues that need consideration, such as bed availability to ensure timely treatment, laboratory support for special testing, and diagnostic imaging. Industry sponsors confirm facility compliance through site selection and initiation visits. In the cooperative group model, specific standards are delineated for institutional membership, ensuring availability and access to appropriate quality standards and accreditations.

Compliance—GCP requires that trials be conducted in compliance with the approved protocol, including eligibility criteria, adverse event monitoring, treatment and modifications. Deviations are permitted only if they are necessary to eliminate an immediate hazard to a

subject. If such situations arise, the deviations must be documented in the subject's medical record and the sponsor and local IRB/REB informed.

Clinicians must recognize that in treating a patient on a therapeutic protocol they are acting both as investigator and as treating physician. The protocol must be followed exactly, adhering to the specified observations and procedures and to their specified timing. This is true at time of entry to the study to determine eligibility, during the delivery of therapy to understand the response and effects of the therapy, and during the protocol-mandated follow-up phase. While it is acceptable to carry out testing additional to that required by protocol, it is not acceptable to disregard the required testing. Further, if a test or procedure is not performed to evaluate an adverse event, that does not signify the absence of an adverse event. Sponsors monitor both the tests and procedures performed and their timing; nonadherence to either is considered a protocol deviation.

The investigator must ensure compliance with study randomization procedures. While the study is ongoing, the randomization code for an individual subject may be broken only as delineated in the protocol, for example, in the case of an adverse event that compromises the health or welfare of the participant. All instances of unblinding must be documented and reported to the sponsor.

Investigational Product—Investigators must be familiar with the use of the investigational product/s in a study. Information is made available through the sponsor-provided IB, which by regulation must be updated annually to include all new information.

The Investigator, while responsible for investigational product accountability at the site, may assign these duties to a pharmacist. A key component of successful GCP is excellent communication between the investigator and the pharmacist, often facilitated by the CRA. Records documenting delivery of investigational product to the site, ongoing inventory, disposition to research subjects and disposition of unused product must be maintained in accordance with the sponsor's requirements, including the ability to track by batch or serial number all investigational products given to individual patients. A common tool used to fulfill these requirements is a DARF (Drug/Agent Accountability Record Form). Investigational product can be used only by official study patients and must be used in accordance with the approved protocol. In studies of drugs that are commercially available, a common deficiency is the use of incorrect drug supply. GCP also requires the investigator or a designee to explain the correct use of the investigational product to subjects and re-confirm understanding at intervals.

The sponsor will provide drug information for all study medications, including formulation, storage requirements, known toxicities, drug stability, administration information, and the supplier of the medication (which may be the sponsor, as in NCI-held INDs, or a commercial source if the medication is not investigational).

Recording and Reporting of Trials—The task of data collection at the sites is generally shared. Investigators produce the source information from which CRAs abstract appropriate information for case report forms (CRF). In creating the source information, investigators must ensure that they document not only routine patient care information but also protocol-specific information such as performance status and toxicity grade and attribution. Important also is the timeliness of alerting the CRA to special circumstances that require reporting, such as disease relapse or progression or serious adverse events.

All documentation must stem from source documents, defined as all information contained in the official medical record or research record as well as any study-related correspondence. In

abstracting data for clinical research, CRAs require a source document. “If it is not written down, it did not happen” is a common creed among CRAs who recognize the importance of source documents.

The investigator must ensure that data submitted to the sponsor are accurate, complete, and timely. If there are discrepancies between the data and the source document, an explanation must be included. If changes are required after data are submitted, modifications should be made without obscuring the initial entry and should be dated, initialed and explained. Obliterating or destroying data or back-dating information could be construed as scientific misconduct.

Adverse Events and Safety Reports—Adverse event recording and reporting is a fundamental aspect of drug development and of human subject protection. The clinical investigator identifies, evaluates, and documents adverse events experienced by study participants at his or her site and informs the sponsor and the IRB/REB. The sponsor is responsible for submitting safety information to the FDA and other regulatory agencies. The NCI uses the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 [10]. The CTCAE has objective criteria such as laboratory values and subjective criteria that require description by investigators using CTCAE-specific language. Adverse event reporting can require documentation of the event from inception to resolution. One of five grades is assigned to an adverse event. Grades 1−3 designate mild, moderate and severe AE; grade 4, life-threatening, or disabling AE; and grade 5, death. Serious adverse events require or prolong hospitalization, are life threatening, or cause significant disability or incapacity, congenital anomaly, birth defect, or death. It is the investigator's responsibility to assess adverse events, determine their grade, attribution, and relationship to the investigational product and report in the appropriate manner to the sponsor and the local IRB/REB.

The sponsor reviews serious adverse event reports and shares information about serious, unexpected events with other investigators in the study or investigating the same drug, in the form of a safety report. In pediatrics it is not uncommon to receive safety reports describing adverse events in elderly patients receiving the same drug on a different study and/or for a different indication. Safety reports must be submitted by the investigator to the local IRB/REB. The sponsor must also submit a summary of the most frequent and the most serious adverse events in an annual report as part of their investigational drug application (IND).

All serious, unexpected adverse events must be reported to regulatory agencies within 15 days of receipt of the information. Any unexpected life-threatening or fatal event must be reported by telephone (or facsimile) within 7 days of receipt. Although causality assessment is integral to reporting, a determination that a given medicinal product caused or was associated with an adverse event is not always possible. Randomized, controlled trials offer the most reliable assessment of the contribution of a test article to an adverse event. Causality is difficult to determine in other settings because of co-morbidity and concomitant medications. Regardless of its cause, the event should be reported within the specified time frame unless there is no reasonable possibility that the drug was associated with the adverse event.

For reporting, CRAs abstract the details of adverse events from source documents. Each protocol defines which grades of adverse events require routine versus expedited reporting. Continuous collaboration between investigators and CRAs is imperative to ensure complete, timely adverse event reporting.

Essential Documents—GCP defines essential documents as “documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor

with the standards of GCP and with all applicable regulatory requirements." Essential documents for clinical trials include:

- Investigator's brochure with updates
- Protocol with amendments
- Date-documented IRB approvals
- CVs of study investigators
- Normal laboratory ranges
- Investigational agent documentation and accountability
- Monitoring reports
- Signed informed consents
- Source documents
- Complete CRFs with documentation of corrections
- Serious Adverse Event notifications
- Safety reports and annual reports to IRB/REB

Monitoring and Auditing—Although the purposes of monitoring and auditing are similar (to assure appropriate trial conduct and data validity), their approaches differ. The ICH GCP document defines monitoring as "the act of overseeing the progress of the clinical trial and ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, GCP, and applicable regulatory requirements." Medical monitors, usually employees of the sponsor, perform on-site (and, if indicated, off-site) evaluations of trial-related activities. The extent and frequency of monitoring should be appropriate for the length, complexity, and other particulars of the trial. Among other duties, the monitor identifies deviations in protocol conduct so that the sponsor may take appropriate corrective steps, e.g., retraining investigators or closing certain sites.

Auditing is defined in the ICH CGP document as "the systematic and independent examination of trial-related activities and documents." The audit is usually conducted at the conclusion of the trial. The sponsor may hire field auditors who document findings in a written report to the sponsor. FDA inspectors also conduct independent study audits. Traditionally, the purpose of FDA audits has been to verify data submitted in support of a marketing application. However, the FDA and the sponsor may conduct "for cause" or directed audits at any stage of investigation if there is reason to suspect a problem with trial conduct or data integrity.

An additional human subject protection is use of a Data Monitoring Committee (DMC) to evaluate accumulating data in a clinical trial [7]. Generally, the sponsor establishes the DMC, selects the members and devises its charter. DMC members should be independent of the sponsor and clinical investigators. The DMC's role depends on the charter and the nature of the study. The DMC is usually empowered to recommend study modifications to enhance participant safety and in some case may recommend that a study be stopped if accumulating data indicate futility or a major safety concern. DMCs review submitted data but, unlike study monitors, do not visit sites to confirm that the data are accurate, the protocol is followed, consent is documented, etc.

Inherent checks and balances exist when the sponsor is not the investigator. When the sponsor is also the investigator, external oversight of the trial is advisable. Individual physicians who

assume the role of sponsor, investigator, or sponsor/investigator should be familiar with guidance and federal regulations that set out the respective duties.

III. Considerations in Trial Design Methodology

The key elements of trial design include defining an appropriate patient population; outlining clear objectives; defining the specific treatment plan, including dosing and dose modification parameters; incorporating appropriate safety and efficacy monitoring; and using accepted statistical methods for hypothesis testing. Pediatric oncology trial designs vary depending on the immediate goals, stage of development of the drug if an investigational drug is involved, and the ultimate goal of the drug development plan.

Phases of Trials—Three phases of clinical trials are customarily conducted in the development of new treatment approaches for pediatric malignancies. These are also summarized in Table 4 .

Phase 1—The initial clinical trials of anti-cancer agents (phase 1 trials) evaluate doses and schedules appropriate for further development. These are typically open-label single-arm trials in patients with advanced/refractory malignancies for which there are no known effective therapies.

If no prior human data is available, the starting dose and schedule for such studies is based on non-clinical data derived from toxicology studies, usually in at least two relevant animal species. However, anticancer agents are usually tested in children only after adult studies. Therefore, the starting dose and schedule can often be based on prior human experience; starting doses are typically 80% of the maximum tolerated dose (MTD) in adults with cancer [11,12].

Phase I studies establish the dose-limiting toxicity (DLT) of investigational agents; the DLT is unacceptably severe toxicity that prevents the use of higher doses. The MTD, usually the dose immediately below that which caused DLT, is used in phase 2 trials.

This phase 1 dose-finding model is based on the assumption that the highest safe dose of a cytotoxic agent is most likely to demonstrate activity and efficacy in later stages of drug development. However, a different endpoint may be appropriate for biologically-targeted therapies, e.g. the effect of a given dose on a biologic disease parameter. This dose is referred to as the optimal biologic dose (OBD) and may be lower than the MTD [13,14].

Phase 2—After an appropriate dose and schedule are identified, antitumor activity is assessed in phase 2 trials. These are usually open-label, single-arm trials. For solid tumors, the primary endpoint of interest is objective tumor response as measured by radiologic criteria_[15]. For hematologic malignancies, remission induction or re-induction is a common goal.

The two-stage design is widely used for phase 2 trials. The sample size in the first stage is designed to confirm a minimum response rate, and the second stage is conducted only if this level of activity is observed. This method limits the number of patients exposed to drugs with poor activity. From a broader perspective, it allows the re-distribution of resources to other agents with greater promise [16].

Randomized phase 2 trials are increasingly being conducted. One rationale is to define an optimal dose for further development. A randomized phase 2 trial comparing the activity and toxicity of two doses of a single drug can be helpful. As “targeted” drugs with non-cytotoxic effects are developed, radiologic tumor response criteria may be of limited value. If these agents stabilize disease rather than significantly reduce tumor size, evaluation of the time to

progression or of progression-free survival is more informative. Such an endpoint, even in preliminary studies, is best assessed in a randomized setting, where bias can be minimized.

Phase 3—Randomized phase 3 trials are usually undertaken to demonstrate the efficacy and safety of a specific drug or treatment approach. Although the primary focus may be a new agent, multimodality therapy regimens (including combination chemotherapy) are often investigated. Therefore, advances in treatment often require randomized trials that explore additions or substitutions to regimens that may improve efficacy or reduce toxicity. Important elements of phase 3 trial design are discussed below.

Trial Objectives—It is important to clearly specify trial objectives that address relevant clinical and scientific questions appropriate to the stage of clinical development and patient population. It is also important to distinguish primary objectives (e.g., defining the MTD in phase 1 studies or evaluating objective tumor responses in phase 2 trials) from secondary objectives, such as assessing the role of a biomarker in predicting outcome. This distinction is important in all stages of development for several reasons, including the relationship of the primary objectives to the statistical components of trial design (e.g. sample size, which is based on the primary objective) and the allocation of resources to priority endpoints.

Prioritization of resources is a significant concern in designing pediatric oncology trials because the number of patients available for enrollment is often inadequate to test multiple hypotheses. Only about 13,000 new pediatric malignancies are diagnosed in the United States each year, in contrast to more than 1.2 million new adult malignancies, excluding skin cancers. Several pediatric solid tumors (neuroblastoma, osteosarcoma) are diagnosed in only a few hundred patients per year.

Common efficacy endpoints in pediatric oncology trials include survival, event-free survival, time to progression or progression-free survival, and objective tumor response rate. A more detailed discussion of these endpoints and of safety endpoints follows.

Subject Selection—The intended patient population for any clinical trial must be clearly defined through eligibility inclusion and exclusion criteria. In pediatric oncology trials, documentation of the histologic diagnosis is usually required. When tumor tissue cannot be obtained without great risk to the patient, other diagnostic tools can be used. One example is brainstem gliomas, whose diagnosis is usually based on a combination of clinical and radiologic findings. Additional pathologic evaluation is playing an increasing role in cancer diagnosis in general, especially in eligibility for pediatric oncology studies. Immunohistochemistry for cytogenetics and cell surface markers is a routine component of the diagnosis and staging of pediatric leukemias and lymphomas. The distinction between small round blue cell tumors of childhood (neuroblastoma, rhabdomyosarcoma, non-Hodgkin's lymphoma, Ewing tumors) relies on immunohistochemical testing and, more recently, cDNA expression profiling, as well as clinical findings [17].

Eligibility criteria should include clinical parameters that define the patient population. These may include age, disease stage, and extent of prior therapy. Laboratory parameters for defining adequate organ function often focus on bone marrow, renal, and liver function, which are affected by many chemotherapy regimens. Some regimens require additional attention to baseline organ function. For example, children who will receive anthracyclines should have evidence of adequate ventricular ejection fraction as measured by a multiple gated acquisition (MUGA) scan or echocardiogram. Some baseline eligibility requirements require pediatric-specific tools. The performance status of children can be evaluated by using a play-performance scale commonly known as the Lansky scale, which is concise and uses parents as observer-

reporters [18]. Some of the baseline assessment tools are also used to monitor children with cancer during the course of a clinical trial.

Randomization—Single-arm trials that use historical controls for comparison can be misleading if there are differences in patient characteristics (age, performance status, prior therapy, staging, supportive care, follow-up). Even when matched historical or concurrent controls can be selected, unknown factors may be unevenly distributed between two groups. Randomization can help to minimize potential bias caused by such factors. When prognostic factors are known, these must be taken into consideration when comparing outcomes between study arms. A stratification process at the time of randomization can distribute prognostic factors evenly between treatment arms. The categories used to define a stratification factor must be mutually exclusive (e.g., age $\geq$ 5 years vs. age < 5 years) and must be known at the time of diagnosis [19].

Randomized trials offer other advantages. For example, efficacy can be evaluated on the basis of time-to-event endpoints such as overall or event-free survival, and safety is evaluated most thoroughly by randomization to placebo and active comparator arms.

Blinding—Blinding of subject assignment in a randomized trial is used to minimize bias. Cancer clinical trials, including those conducted in children, have not routinely used this strategy. The toxicity profile of many cancer drugs and the different schedules and routes of administration used make blinding difficult. Orally administered forms of several new drugs with limited toxicity have allowed blinding in some cases [20].

Upfront Investigational Window Studies—When existing data support the evaluation of drug activity in a population not eligible for a phase 1 dose-finding study (e.g., when therapy that provides a benefit is available), an upfront window study design may be appropriate. The agent's activity can be assessed in the “upfront window” before standard therapy in newly diagnosed patients with high-risk disease, if mechanisms are in place to assure safety and to ensure that the benefits of standard therapy are not compromised. Patients who respond can then receive the newer agent along with the standard combination chemotherapy to evaluate the effect on survival or disease-free survival. This approach has been used to evaluate the introduction of topotecan and irinotecan into treatment regimens for metastatic neuroblastoma and rhabdomyosarcoma [21-23].

Efficacy Assessment—Assessment of clinical efficacy in pediatric oncology trials may involve a number of endpoints, depending on the diagnosis, stage of development of the drug, and nature of the expected drug effect. Endpoints commonly used include those related to direct tumor kill, such as the radiologically measured objective response rate, or time-to-event endpoints such as progression–free survival. The most commonly examined endpoints are discussed below.

Overall Survival—Overall survival, defined as time from randomization to death from any cause, is often measured in randomized phase III trials. Survival can be continuously assessed through contact during hospitalizations or office visits or by telephone. The date of death can easily be confirmed and is independent of causality. However, this endpoint has some limitations, including the need for a relatively larger sample size, potential confounding by cross-over treatments, and a relatively long period of follow-up. In pediatric oncology, limitations of sample size and follow-up can be problematic, especially given the small number of patients available for enrollment. In addition, dramatic improvement of survival of some diseases over the past several decades has altered their natural history, and many years of follow-up would be required for a mature analysis of overall survival.

Event-Free Survival—Event-free survival is an endpoint often used in pediatric cancer trials. It is defined as the time from randomization to occurrence of a major adverse clinical event such as failure to achieve remission, relapse, and death during remission. This endpoint has been used in studies of pediatric leukemias and solid tumors to overcome some of the limitations of an overall survival endpoint [14].

Objective Tumor Response—Objective tumor response, defined as a reduction in solid tumor size, is usually evaluated in the phase II setting. This endpoint provides initial evidence of a treatment's biologic activity. Tumor response is also a secondary endpoint in many phase III trials, allowing evaluation of response in a more homogeneous, less treatment-refractory population. Unlike time-to-event endpoints, which are affected by both the treatment and the natural history of the disease, tumor response can usually be attributed entirely to treatment in single-agent studies or in randomized studies comparing a standard regimen to the standard regimen plus the new treatment.

Safety Assessment—In trials with a primary objective of assessing efficacy, secondary objectives may include evaluation of safety parameters. Regardless of stated primary and secondary objectives, pediatric oncology trials routinely include elements of safety monitoring. These focus primarily on laboratory and clinical monitoring of bone marrow, hepatic, renal, and when appropriate, pulmonary and cardiac function. The frequency and nature of monitoring depends on the treatment regimen being evaluated.

Pediatric cancer trials often utilize NCI criteria for grading of adverse reactions. The original criteria were developed in 1982 for use in adverse drug experience reporting, study adverse events summaries, reports to the FDA, and publications. The criteria have undergone several revisions. Version 3.0, the Common Terminology Criteria for Adverse Events, published in 2003 [24], reflects feedback from the pharmaceutical industry, regulatory agencies, and cancer cooperative groups. Version 3.0 includes new guidelines for late effects, surgical and pediatric effects, and multimodality issues, and for reporting duration of an effect [10]. The occurrence, frequency and severity of these effects are considered in treatment decisions, with clear criteria prespecified for dose interruption, dose modification, or treatment cessation.

Safety endpoints are increasingly an integral part of pediatric cancer trials, especially when current treatments provide significant benefit. The goal has shifted to maintaining the efficacy of existing therapies while minimizing short-term and long-term toxicity. For example, the National Wilms Tumor Study Group has demonstrated that radiation therapy can be safely eliminated for stage I and II Wilms tumor [6]. Endpoints for evaluating long-term toxicity include neurocognitive, immune, and cardiac function, occurrence of second malignancies, fertility, and psycho-social factors.

IV. A Regulatory Perspective: the IND, NDA, and Biological License Application Process

The path from drug discovery to marketing takes many years and many dollars. The FDA's involvement usually begins after the research and discovery phase and prior to the first human studies (“first-in-man” studies). The sponsor of the investigational drug or biologic commonly requests a pre-IND meeting. During the meeting, the FDA provides feedback about the manufacturing process (Chemistry/Manufacturing/Controls or CMC), in vitro and animal studies, and the proposed clinical trial. The sponsor must submit an IND application to conduct clinical studies of the drug or biologic. The agency reviews the application and determines within 30 days whether the study can proceed. The FDA may impose a Clinical Hold (halt or delay the start of a clinical study). In that event, the FDA must provide the sponsor written communication of the IND deficiencies within a specified period. The FDA lifts the Clinical Hold when (or if) the sponsor satisfactorily addresses the deficiencies. INDs generally undergo

numerous amendments covering manufacturing, non-clinical, and clinical aspects of the product testing, including safety reports and an annual summary of activity.

The initial IND submission for the first human studies of a product usually contains a clinical phase I protocol. After phase 2 and 3 studies, the sponsor generally submits an application to market the drug (a New Drug Application [NDA] or a Biological License Application [BLA]). The FDA must review the complete marketing application within 6 months for a priority application and 10 months for a standard application. Agency personnel may conclude that the product it is safe and effective for its intended use and grant market approval or may identify deficiencies that require submission of additional data. Phase 4 studies are those conducted after marketing approval. While the FDA tracks the progress of these post-marketing commitment (PMC) studies, most are not required by law [25] and there is no penalty for failure to comply. The two exceptions where these studies are required are the PMCs for drugs and biologics granted accelerated approval and PMCs to study the drug or biological under the Pediatric Research Equity Act (PREA).

Accelerated approval may be granted for drugs or biologics intended to treat a serious disease for which there is no existing or comparable therapy. In such cases, the FDA may approve the product on the basis of data on a surrogate endpoint that predict “reasonably likely” clinical benefit. The sponsor must complete a clinical study or studies to verify and describe the clinical benefit. The FDA may, after a hearing, take the product off the market if the sponsor fails to complete the required PMC study or if the study fails to confirm benefit.

V. History and Present Status of Drug Development Regulations

The FDA's statutory authority began with the 1906 Pure Food and Drugs Act prohibiting interstate commerce of misbranded food and drugs. Over the years, often as the result of medical mishaps, Congress passed additional reform legislation. In the mid-1930s, several children died after being given elixir of sulfanilamide, and Congress passed the 1938 Food, Drug and Cosmetic Act requiring proof of safety before marketing. After thalidomide caused birth defects, Congress passed the 1962 Kefauver-Harris amendment requiring proof of efficacy; this legislation gave rise to new regulations governing investigational products (the IND regulations). Biological product legislation developed in parallel. After the deaths of several children who received contaminated diphtheria anti-toxin, the 1902 Biologics Control Act imposed conditions on the manufacture of vaccines, toxins, and anti-toxins. Biologics facility inspections were required starting in 1955 after more than 200 cases of polio and 11 deaths from inappropriate poliovirus inactivation during vaccine manufacture. Biological products were initially regulated by the National Institutes of Health. In 1972 oversight was transferred to the FDA. New statutes and regulations during and after the 1990s specifically addressed and encouraged pediatric studies. Table 5 summarizes important milestones in pediatric drug development.

The 1997 FDA Modernization Act (FDAMA) added a pediatric exclusivity provision to the regulations [18] that provided drug manufacturers an economic incentive of 6 months marketing exclusivity in return for conducting studies in pediatric populations. The pediatric studies had to be consistent with an FDA legal document, the Written Request (WR) which stipulates study requirements. Data from the studies must be submitted before the existing patent expires [26]. New regulations also specified that every new drug or biologic product (or any new indication or dosage) must be studied in children. This regulation, “the Pediatric Rule,” became final in 1998 [27]. Unlike the exclusivity provision, it required studies and did not provide financial incentives.

The exclusivity provision and the Pediatric Rule increased the number of pediatric studies. Exclusivity was due to expire in 2002 [28], but its positive results led to the 2002 Best

Pharmaceuticals for Children Act (BPCA) [29]. BPCA renewed exclusivity for an additional 5 years, provided a mechanism for study of drugs no longer under patent, and established the Pediatric Subcommittee of the Oncology Drugs Advisory Committee (ODAC). This Subcommittee iscomposed of experts in pediatric oncology and other fields (e.g., statisticians) and patient, consumer, and industry representatives. The ODAC is a forum for discussion of pediatric oncology drug development. It has recently discussed such topics as endpoints for trials of new drugs to treat pediatric brain tumors, the FDA process for handling drug shortages, off-patent oncology drugs for which pediatric studies are needed, safety monitoring of clinical studies enrolling children, and age-appropriate formulations for use in pediatric oncology.

The Pediatric Rule, understandably less popular than exclusivity in the regulated industry, underwent legal challenge, and the U.S. District Court enjoined FDA from enforcing the rule. However, in 2003, Congress passed the Pediatric Research Equity Act (PREA), which reiterates many of the Pediatric Rule principles [30]. Table 6 compares the two laws. Pediatric studies required under PREA, if not completed when the product comes to market, become required PMCs. Failure to conduct or complete these studies can result in economic penalties.

Today, BPCA and its predecessor (pediatric exclusivity provisions under FDAMA) and PREA and its predecessor (the Pediatric Rule) are the stimuli (the carrot in the case of BPCA, the stick in the case of PREA) for pediatric studies. Since their inception, the FDA has seen hundreds of pediatric studies enrolling thousands of patients and, more importantly, more than 100 drug labels contain new prescribing information for children [31,32].

With the exception of supportive care and some forms of leukemia, most drugs approved for adult cancer are not relevant to pediatric patients, and required studies under PREA are waived. Although pediatric patients with cancer gain little from PREA, new insights into oncogenesis may one day allow a molecular grouping of cancers (e.g., epidermal growth factor receptor–expressing tumors) that will show whether certain pediatric and adult malignancies are sufficiently similar that PREA may be applicable.

During the early years of exclusivity, there was little rationale for pediatric research with drugs approved for adults. However, because BPCA is voluntary and is associated with incentives, many manufacturers were interested in evaluating their adult-cancer drugs in pediatric cancers. In 2000, the FDA issued guidance on studies that could lead to exclusivity for pediatric oncology settings [33]. Since 2000, FDA has issued Written Requests to manufacturers to study pediatric malignancies. To date, 11 drugs studied in pediatric malignancies have received exclusivity, and in 9, the information was included in the drug labeling. These data were presented at the June 2007 meeting of the Pediatric Oncology Subcommittee to the Oncology Drugs Advisory Committee (Transcripts of the June 27, 2007 Pediatric Oncology Subcommittee of the Oncology Drugs Advisory Committee, Rockville, MD). BPCA also included provisions for the study of certain older, off-patent drugs, which are identified and prioritized by an expert panel of pediatric sub-specialists. At present, the five off-patent oncology drugs on the priority list are vincristine, daunomycin, actinomycin D, methotrexate and isotretinoin.

In January 2007 new legislation governing the development and authorization of medicines for use in children was introduced in the European Union (EU). Regulation (EC) No. 1901/2006 as amended (the “Paediatric Regulation”) introduces sweeping changes into the regulatory environment for pediatric medicines to better protect the health of children in the EU. The Paediatric Regulation also brings many new tasks and responsibilities to the European Medicines Agency (EMA), chief of which is the creation and operation of a Pediatric Committee within the EMA to provide objective scientific opinions on any development plan for medicines for use in children [34].

Summary

Pediatric oncologists have a duty and responsibility to advance the care of our patients through scientifically and ethically valid clinical research. Such research has been a cornerstone of the dramatic progress in curing childhood cancer. Central to this success is the conduct of clinical investigations adhering to principles of good clinical practice. Ultimately, this is an activity sanctioned by laws, regulations and guidance that carries with it the responsibility of public trust.

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Table 1

Summary of commonly referenced International Conference on Harmonization (ICH) clinical efficacy guidelines

Document	Subject	Content
ICH E 2	Adverse Event Reporting	Defines terms, timeframes for AE reporting and formatting of AE reports
ICH E 6	GCP Consolidated Guidelines	Defines responsibilities of sponsors, investigators, consent process monitoring and auditing procedures, and protection of human subjects
ICH E 9	Statistical Principles	Design and conduct of trials intended to support or establish efficacy
ICH E 10	Choice of Control Groups	Properties and limitations of different kinds of control groups (active control equivalence, non-inferiority, etc.)
ICH E 11	Clinical Investigations in Pediatric Population	Principles of clinical investigations in children, including timing of studies and extrapolation of data relative to studies conducted in adults, consent, assent, and interventions
ICH E 14	Evaluation of QT/QTc Interval Prolongation	Testing the effects of new agents on the QT/QTc interval as well as cardiovascular adverse events

Table 2

U.S. Food and Drug Administration regulations related to good clinical practice and clinical trials

21 CFR Part 11	Electronic Records; Electronic Signatures
21 CFR Part 50	Human Subject Protection (Informed Consent)
21 CFR Part 50, subpart D	Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products
21 CFR Part 54	Financial Disclosure by Clinical Investigators
21 CFR Part 56	Institutional Review Boards
21 CFR Part 312	Investigational New Drug Application
Forms 1571 and 1572	Investigational New Drug Application and Statement of Investigator
21 CFR Part 314	Applications for FDA Approval to Market a New Drug
21 CFR Part 601	Applications for FDA Approval of a Biologic License
21 CFR Part 812	Investigational Device Exemptions
21 CFR Part 814	Premarket Approval of Medical Devices

Table 3

Required elements of an informed consent document

Statements that indicate:
1. Study involves research; purposes, expected duration, description of study procedures and identification of experimental procedures
2. Description of foreseeable risks or discomforts
3. Description of reasonably expected benefits to subjects or others
4. Disclosure of procedures or treatments
5. Extent of confidentiality of records that can be expected
6. Explanation of availability of treatment and/or compensation for injuries from the research
7. Contact information for research questions, subjects rights and research-related injury
8. Statement that participation is voluntary, no penalty or loss of benefits for refusal, ability to discontinue participation at any time

Table 4

Phases of Clinical Development

Phase	Phase 1	Phase 2	Phase 3
Goals	Dose finding, safety	Activity	Safety and efficacy
Population	Refractory	Less refractory, Newly diagnosed with high-risk features	Newly diagnosed
Randomization	No	Yes or no	Yes
Typical sample size	Up to 30	20−50	100 or greater
Typical endpoints	Dose-limiting toxicity, maximum tolerated dose, optimal biologic dose, pharmacokinetics	Objective response rate, remission rate	Overall survival, event-free survival, remission rate

Table 5

Milestones in Pediatric Drug Development

- 1977 — American Academy of Pediatrics Committee on Drugs - Report on study of drugs in children
- 1979 — FDA articulates how to provide information on Labeling
- 1997 — FDAMA/Exclusivity Provision
- 1998 — Pediatric Rule Regulation (enjoined 2002)
- 2001 — Subpart D regulations (adoption by FDA)
- 2002 — Best Pharmaceuticals for Children (BPCA)
- 2003 — Pediatric Research Equity (PREA)
- 2007 — BPCA and PREA sunset

Table 6

Comparison of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act

BPCA	PREA
Voluntary, financial incentives	Required, no financial incentive
Includes orphan indication	Orphan indications exempt
Studies: whole moiety, other indications	Only drug/indication under development
Applies only to drugs	Applies to drugs and biologicals
Trigger — Written Request	Trigger — Marketing application
Results posted regardless of approval	Results confidential if not approved
Safety data reviewed 1 year later	Standard safety reporting