



## Committee on Clinical Investigation: Autonomy and Functions

### Policy

Children's Hospital has established an Institutional Review Board (IRB) designated the Committee on Clinical Investigation (CCI). The CCI is responsible for reviewing "research with human subjects," as defined by the Department of Health and Human Services, and "clinical investigation," as defined by the Food and Drug Administration (FDA). (see CI policy: **Definition of Human Subject and Research** for further guidance.) To accomplish this goal, the CCI reviews research protocols to consider those issues in design and conduct that could potentially affect the safety, rights, and welfare of human subjects. The CCI has as its primary responsibility the protection of research subjects. There is no individual, group of individuals, or entity within or outside Children's Hospital that can override a decision of the CCI, except to add restrictions or to disapprove an already approved activity. The CCI must function independently of other entities in the organization.

### Purpose

The purpose of this policy is to describe the areas considered during the CCI review process, which allow the CCI to ensure the protection of human subjects and its ability to remain autonomous. The different categories of review are described, followed by a listing of some of the major issues that are considered. The list of issues is by no means complete, and is to serve as a guideline only.

### Procedures

#### Authority of the Committee on Clinical Investigation

Children's Hospital grants the Committee on Clinical Investigation the following authority:

- To approve, require modifications to secure approval, or disapprove all research activities overseen and conducted by the organization;
- To suspend or terminate approval of research that is not being conducted in accordance with CCI requirements or that is associated with unexpected serious harm to participants;
- To observe, or have a third party observe, the consent process; and
- To observe, or have a third party observe, the conduct of the research.

Officials of Children's Hospital may not approve any research that has not been approved by the Committee on Clinical Investigation.

## **Independence of the Committee on Clinical Investigation**

No individual or group of individuals may inappropriately try to influence the deliberations and decisions of the Committee on Clinical Investigation. Any IRB member may report any attempt to influence the decision of the Committee on Clinical Investigation to the Vice President of Research Administration and the President of Children's Hospital. The Vice President Research Administration and the President of Children's Hospital will investigate and resolve the incident so there is no undue influence placed on the Committee activities and determinations.

## **Specific Categories of Functions**

(This is an abbreviated version. For more complete criteria, see the CCI reviewer worksheets.)

### **Scientific Review and Merit**

The CCI has the authority to examine the scientific study design to determine its impact on the rights and welfare of human subjects. Although each department is required to establish a scientific review process, the CCI also reserves the right to review the science as it impacts the risk/benefit assessment and human subject protections.

- Are the specific aims clearly defined and specified?
- Are there adequate preliminary data to support the conduct of the protocol?
- Is there appropriate justification for the research?
- Is the proposed design adequate to answer the questions being asked?
- Are the objectives likely to be achievable within the conduct of the protocol?
- Are any plans for randomization and/or placebo and control arms described and justified?

### **Principal Investigator (PI) and Research Staff *Qualifications***

The CCI considers the qualifications of the PI when reviewing protocols. It is also the responsibility of the Department Chair or Division Chief to confirm, as part of his or her sign off on the protocol, appropriate PI and research staff credentials, as this type of information is most accessible to the Department Chair or Division Chief. The CCI may ask for any type of information it requires on individuals listed as investigators or research support staff in order to verify that the individuals have the appropriate qualifications and expertise to conduct the research safely.

## **Resources**

The CCI takes into consideration the resources available to ensure that all aspects of the project and follow-up are conducted rigorously and with due regard for the safety and well being of the research subjects.

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- Are there appropriate resources (e.g., equipment, lab capacity, space) to ensure the optimal safety of the research subjects?
- Does the investigator have the resources to assure the appropriate monitoring of subjects during and after the research?
- Is there a possible need for counseling or support services during and/or as a result of the study; and, if so, are these resources available?
- Are there provisions for research related injuries?

### **Equitable Selection of Subjects and Inclusion/Exclusion Criteria**

The CCI determines whether the selection of subjects is equitable. In making this determination, the Committee must be certain there is a fair sharing of the burdens and benefits of the research.

- Is the subject population selected so that the burdens fall on those most likely to benefit?
- Does the nature of the research justify the proposed subject population?
- Are the criteria for the source of subjects clear and defined?
- Have the inclusion and exclusion criteria taken into consideration subject safety and welfare concerns?
- If women, children, or minorities are excluded, has this been adequately justified?
- What provisions are made to include non-English speaking individuals? If they are excluded, is there adequate justification?
- Are there adequate data to permit the inclusion of children/adolescents?

### **Recruitment**

The CCI reviews the procedures utilized to recruit research subjects. Such procedures include any type of posting, flyer, notice, letter, and approaching research subjects for the purpose of recruiting for the research.

- Are the methods for recruitment clearly defined?
- Are the timing and location for recruitment acceptable?
- Are the recruitment materials clear and comprehensive, and do they not overstate the benefits of the research?
- Are there acceptable procedures for screening subjects prior to recruitment?
- If recruitment must occur during a critical or stressful period, what precautions have been taken to eliminate potential coercion?
- Have the recruitment materials and practices been developed to avoid undue influence in deciding whether or not to participate?

### **Research Protocol Procedures**

The CCI reviews in detail the procedures required for the conduct of the research protocol to ensure that the risks are minimized and the benefits are maximized. The Committee reviews the procedures to ensure they may be conducted safely, and with appropriate oversight and expertise. The Committee also reviews what will happen with the information collected during the study, and whether there are adequate provisions for follow-up if necessary.

- Is there an adequate rationale for the proposed procedures?
- Has the investigator provided a complete description of the procedures to be performed, including the associated risks and benefits?
- Is there a clear differentiation between those procedures that may be required for standard care and those required for research purposes?
- What will occur with the information the procedures provide?
- Are there plans to inform research subjects about their specific data, and data from the study results in general?
- When appropriate, are the procedures and assessment combined with those that are already performed for diagnostic or treatment purposes?

## **Drug and Device Considerations**

If a research protocol involves the use of drugs, devices, or biologics, the Committee must ensure that the protocol complies with all relevant FDA regulations. Additional detailed CCI policies for investigators and the Committee have been developed for investigational drugs and devices. The following are some of the general issues that are considered by the CCI:

- Is the status of the drug or device adequately described?
- If necessary, is the supporting documentation from the sponsor included with the submission (investigational brochure, package inserts/labeling, FDA letters of determination regarding status of the drug device).
- What have the preclinical or initial clinical trials shown?
- Is the phase of the study (Phase 1, 2, or 3) appropriate for investigational drugs?
- If the study involves a marketed drug/device for an unapproved indication is an IND or IDE necessary?

## **Data Analysis and Data Safety Monitoring Plan**

Although data analysis and the establishment of a data and safety monitoring plan are often reviewed as part of the departmental scientific review process, in order to maximize benefits and minimize potential harm to subjects, the CCI has responsibility for ensuring that the data obtained from the study will be useful. In addition, it is the CCI's responsibility to be certain that an appropriate data and safety monitoring plan exists for all protocols as appropriate for the nature of the study. The following are some considerations:

- Is the rationale for the number of subjects reasonable?
- Are there defined and justified plans for data and statistical monitoring?
- Have endpoints and stopping rules been defined if necessary?
- Are there provisions for a data and safety monitoring plan, and are they appropriate for the conduct of the specific research?

## **Risks and Benefits**

The Committee must determine that the risk to the subject is minimized by implemented procedures that are consistent with sound research design and that do not expose the subject to risk unnecessarily. In evaluating the risks and benefits, the

CCI should consider only those risks and benefits that may result from the research (as distinguished from the risks and benefits of therapies the subject would receive even if not participating in the research). The risk will be reviewed in relation to the benefit the subject will receive. In general the higher the risk the greater the benefit one would expect. The IRB will also consider potential risks to a community that may result from the research for examples stigmatization. The IRB will not consider the long range effects of applying the knowledge gained in the research as among those risks or benefits that fall within the purview of its responsibility.

- Are the risks and benefits well described?
- What are the probability and magnitude of the risks?
- Have the risks been minimized and potential benefits maximized as much as possible?
- Has the possibility of unknown risks been addressed?
- Are there appropriate monitoring procedures to identify risks?
- Are there appropriate mechanisms to address risks if they occur?
- Should the period of initial approval be less than one year in order to monitor for potential risks?

### **Pediatric Considerations**

- As the majority of research at Children's Hospital involves pediatric and adolescent subjects, the CCI is required to make the appropriate risk benefit assessments for compliance with HHS and FDA regulations Subpart D. In addition, the CCI must be assured that there are adequate additional protections for children.
- Has the investigator provided a suggested risk/benefit assessment with appropriate supporting information?
- Does the CCI agree with the risk/benefit determination?
- If the risk is greater than minimal is there a potential for direct benefit, or are the following four conditions met:
  1. the risk represents a minor increase over minimal risk;
  2. the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
  3. the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition that is of vital importance for the understanding or amelioration of the subject's disorder or condition; and
  4. adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

### **Vulnerable Populations**

The federal regulations have special protections for 3 defined vulnerable populations (children, prisoners, pregnant women/fetuses/neonates). The IRB is required to following the required subparts of the federal regulations to address all of the findings required. However, it is important to recognize that many other forms of vulnerability exist. These categories may include socially or economically disenfranchised, decision ally impaired, terminally ill, illiterate subjects, and migrant

workers. The IRB should consider the following issues when conducting review involving these populations

- Are the participants likely to be vulnerable to coercion or undue influence?
- Does the IRB require additional special expertise or consultation to become knowledgeable about the vulnerable population?
- What additional safeguards can the IRB require to be included in the research to protect their rights and welfare?

## **Payments and Costs**

The CCI reviews any payments made to research subjects and any costs the subjects may incur as a result of participating in the research. The CCI must be certain that any payments do not unduly influence a parent, child, or adolescent to participate, and are paid fairly. The CCI must also determine whether any payments are reasonable based upon the complexities and inconveniences of the research.

- Has the investigator appropriately broken down payments to the categories of reimbursement, compensation, tokens of appreciation, and incentives?
- Are the amounts and forms of payments (e.g., gift certificates, toys) reasonable in relation to the research?
- Who receives the payments: the parent and/or child? Is this appropriate?
- Is there a need to prorate any payment if a subject does not complete the trial?
- Are there adequate plans to avoid out of pocket expenses?
- Are there provisions for care and payments in the event of a research related injury?

## **Privacy and Confidentiality**

When appropriate, the CCI must determine that there are adequate provisions for assuring the privacy of research subjects and for maintaining the confidentiality of the research data. The CCI reviews the plans for how privacy is protected and the collection, storage, and analysis of data.

- How will the investigator take into consideration privacy concerns when approaching and involving a research subject?
- Does the investigator take steps to assure privacy?
- How will the research data be collected, recorded, and maintained?
- Are there adequate provisions to protect privacy and confidentiality?
- Are there adequate plans for storing and coding data?
- Has the use of identifiers been eliminated or minimized?
- Has the investigator adequately addressed in the protocol and consent whether research data will be included in a medical record?
- Has the investigator described who will have access to data and under what conditions?
- As necessary, have the HIPAA provisions and requirements been met?

## Consent, Parental Permission, and Assent

The CCI must determine that consent will be sought from each prospective subject or legally authorized representative, and that it will be adequately documented. When children are involved, parental permission will be documented and assent obtained as required by the regulations. The CCI must also determine whether the permission of one or both parents is required. The CCI may waive or alter the procedure for informed consent only when consistent with federal and state regulations. Assent is to be obtained from those children capable of understanding the research and its ramifications, unless the child is not capable, or the intervention involved in the research holds out the prospect for direct benefit that is important to the health and wellbeing of the child and is available only within the context of the research. The CCI will review consent, parental permission and assent documents to be sure that all required regulatory elements are addressed.

### Other Issues

- The CCI may consider any issue or concern it deems necessary in order to adequately protect the rights and welfare of research subjects.
- The CCI may request references, as appropriate, and may consult with any individual it deems necessary in order to assure adequate review.
- As part of its review, the CCI must determine the period of time until the next continuing review. Additional reviews may occur more frequently than once per year, if necessary.

## Related Content

Reviewer Worksheets

## Document Attributes

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