Human Subjects Research

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Objectives

- Discuss the differences and similarities between Clinical Care and Clinical Research
- Define key terms in human subjects research
  - Identify research activities that involve human subjects
- What is the requirements for approval of research at NCHS?
- Discuss differences between research studies & QI projects
- To remind attendees about resources available for research investigators at Nicklaus Children's Hospital

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Clinical Care vs. Clinical Research: Similarities

- The same personnel can sometimes serve in both capacities
- Similar settings – clinics, hospitals, outreach situations
- Treatments, procedures, tools may be the same or similar
- Safety and protection of patients, participants, subjects

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Clinical Care vs. Clinical Research

	Clinical Care	Research
Goal	To provide benefit to the individual	New knowledge for societal benefit
Ethical Principles	• Therapeutic nonmaleficence • Therapeutic beneficence	• Nonmaleficience • Balancing risks/benefits
Duties	• Respond to the patients needs • Act in the patient's best interests	• Answer the research question • Follow the protocol
Documentation	Yes	Yes, Yes, Yes

CROMS and NIDCR "Clinical Care vs. Research" 22Mar2012 and Harvard Catalyst "The History of Research Ethics" 2017

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Clinical Care vs. Clinical Research vs. Quality Improvement

	Clinical Care	Research	Quality Improvement
Goal	To provide benefit to the individual	New knowledge for societal benefit	To improve a program, process or system
Ethical Principles	• Therapeutic nonmaleficence • Therapeutic beneficence	• Nonmaleficience • Balancing risks/benefits	• Nonmaleficience • No increased risk to patients, may benefit patients
Duties	• Respond to the patients needs • Act in the patient's best interests	• Answer the research question • Follow the protocol	• Assessment of program, process or system • Implement any knowledge gained as soon as possible.
Documentation	Yes	Yes, Yes, Yes	Not required by regulations, but always a good idea.

CROMS and NIDCR "Clinical Care vs. Research" 22Mar2012 and Harvard Catalyst "The History of Research Ethics" 2017

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Is my project Human Subjects Research?

3 Key Questions

Answer questions in proper sequence when considering whether an activity is research, human subjects research, or exempt:

1. Is this project **research**?
2. If so, does it involve **human subjects**?
3. If so, is it **exempt**?

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How is Human Subjects Research Defined?

Definition of **Research** [45 CFR 46.102]:

Research is a *systematic* investigation, including research development, testing and evaluation, designed to develop or contribute to *generalizable knowledge.*

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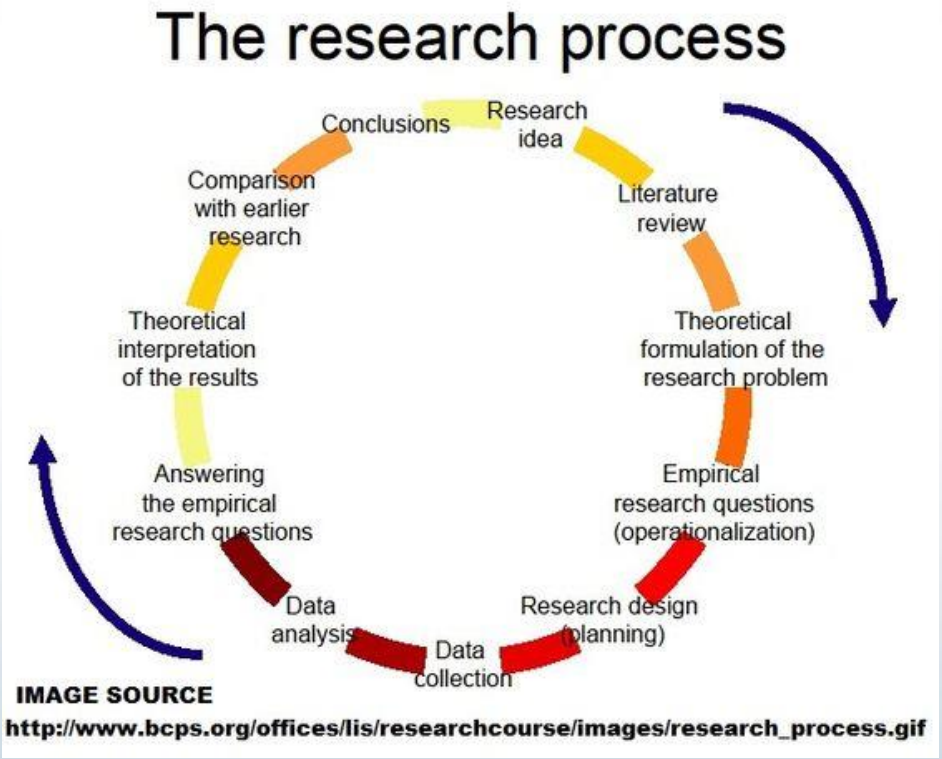
Research is "Systematic."

A ***systematic investigation*** is a project that is planned in advance and that uses data collection and analysis to answer a question*



7 STEPS OF RESEARCH PROCESS

- Step One: Define research problem
- Step Two: Review of literature
- Step Three: Formulate hypotheses
- Step Four: Preparing the research design
- Step Five: Data collection
- Step Six: Data analysis
- Step Seven: Interpretation and report writing

*ORO Presentation on VHA Operations Activities That May Constitute Research (6/18/2010)

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Research is "Generalizable."

Generalizable knowledge is information that expands scientific understanding or the knowledge base of a scholarly field of study

- Activity would be research if:
  - Designed to expand knowledge or understanding about field of study

- Activity would not be research if:
  - Designed solely for NCHS's internal purposes, and
  - Is not designed to be generalized beyond NCHS (i.e. not designed to expand scientific understanding or knowledge of base of a scholarly field of study)

- Activity is always research if:
  - Funded or supported as research
  - Clinical Investigation as defined by the FDA

*ORO Presentation on VHA Operations Activities That May Constitute Research (6/18/2010)

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Case Study # 1

- The University Medical Center (UMC) establishes a special congenital heart clinic
- UMC implements a process to refer patients for special services (e.g., nutrition, physical therapy)
- For internal quality assurance, Nurse Cordoba reviews patient charts to evaluate whether the referral process is working
- She surveys patients to evaluate their satisfaction
- Her activities are not designed to expand scientific understanding or the knowledge base of a scholarly field

Is this Research?

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Case Study # 1: Q & A

Is the nurse conducting a systematic investigation?

- Yes
- Activity planned in advance
- Activity uses data collection and analysis to answer a question

Is this activity designed to develop or contribute to generalizable knowledge?

- No
- Activity is for internal operations
- Will not expand the scientific understanding or the knowledge base of a scholarly field

Is this Research?

- No.
- Knowledge is not generalizable

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Case Study # 2

- Same as Case #1, plus…
- Nurse Cordoba will pull “extra data” not needed for referral review
- She will compare the process to another intervention done at State U Medical Center
- She plans to generalize the findings beyond UMC and hopes to expand the knowledge base of treatments for congenital heart patients

Is this Research?

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Case Study # 2: Q & A

Is this activity designed to develop or contribute to generalizable knowledge?

- Yes
- The information will expand knowledge base of congenital heart patients.

Is this Research?

- Yes
- Meets criteria for “systematic investigation” and “generalizable knowledge”

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Key Questions - In Order

Answer questions in proper sequence when considering whether an activity is research, human subjects research, or exempt:

1. Is this project **research**?
2. If so, does it involve **human subjects**?
3. If so, is it **exempt**?

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Definition

- ***Human subject*** means a living individual about whom an investigator (whether professional or student) conducting research:
  - (i) Obtains information or biospecimens through ***intervention or interaction*** with the individual, and uses, studies, or analyzes the information or biospecimens; **or**
  - (ii) Obtains, uses, studies, analyzes, or generates ***identifiable private information*** or identifiable biospecimens.

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Items to Consider…

- Does the research involve an intervention or interaction with the individuals?
- Does the research involve obtaining information about living individuals?
- Is the information private?
- Is the information individually identifiable?

*OHRP Human Subject Regulations Decision Charts (9/24/2004)
www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm

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More Definitions

- ***Intervention*** includes both physical procedures by which information are gathered (e.g. venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes

- ***Interaction*** includes communication or interpersonal contact between investigator and subject

- ***Private information*** includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).

- ***Identifiable private information*** is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

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Identifiable Private Information protected under the HIPAA Privacy Rule

(1) Names
(2) All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP code, and their equivalent geocodes, except for the initial three digits of the ZIP code…
(3) **All elements of dates (except year)** for dates that are directly related to an individual, including birth date, admission date, discharge date, death date, and all ages over 89 and all elements of dates (including year) indicative of such age…
(4) Telephone numbers
(7) Device identifiers and serial numbers
(8) Email addresses
(9) Web Universal Resource Locators (URLs)
(10) Social security numbers
(11) Internet Protocol (IP) addresses
(12) Medical record numbers
(13) Biometric identifiers, including finger and voice prints
(14) Health plan beneficiary numbers
(15) Full-face photographs and any comparable images
(16) Account numbers
(17) Any other unique identifying number, characteristic, or code,
And 3 more…

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Implications – why does it matter?

Human Subjects Research:

NCHRI must review the activity, as per Nicklaus Children's Health System **policy** (Review of Research at Nicklaus Children's Hospital, http://policies/dotNet/documents/?docid=16888) and per our accreditation as a Human Research Protection Program (HRPP).

Not Human Subjects Research:

Neither NCHRI nor an IRB (Institutional Review Board/Ethics Committee) is required to review the activity. As an HRPP, NCHRI can provide Letters of Determination for non-Human Subjects research studies, if required for publication/presentation, but will require a written project plan/protocol.

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Definitions

- **IRB – Institutional Review Board** – a committee formally constituted and designated to review and approve research involving human subjects with the main objective to protect the rights and welfare of the humans participating as subjects in research studies.
  - Nicklaus Children's Hospital does not have an internal IRB.
  - We rely on a commercial IRB or, for multi-institutional projects, we may rely on another institution's IRB

- **Human Research Protection Program (HRPP)** - comprehensive system to ensure the protection of human subjects participating in research.
  - Nicklaus Children's Hospital is an accredited HRPP.
  - All research must be reviewed by the Nicklaus Children's Hospital Research Institute.

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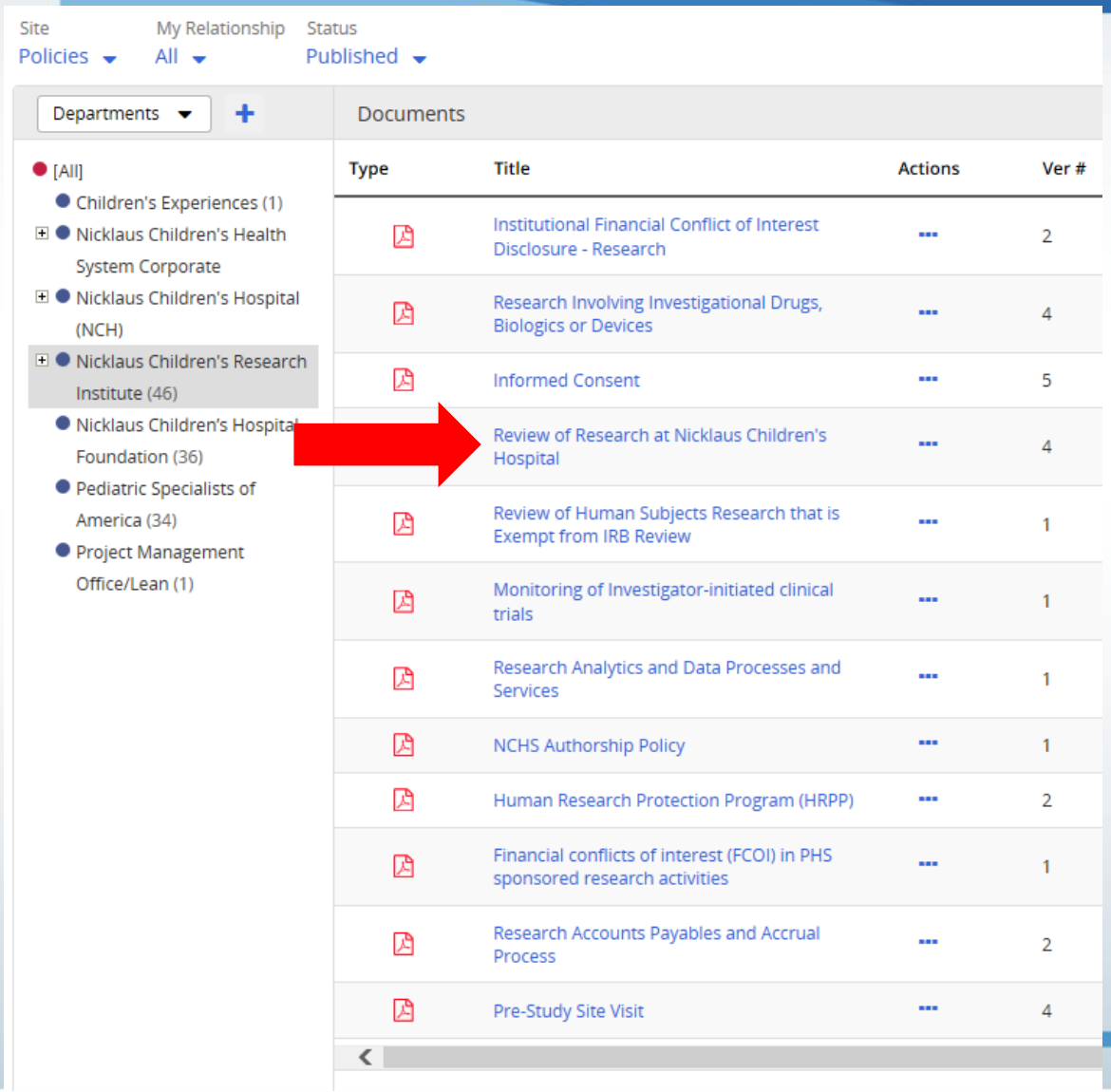
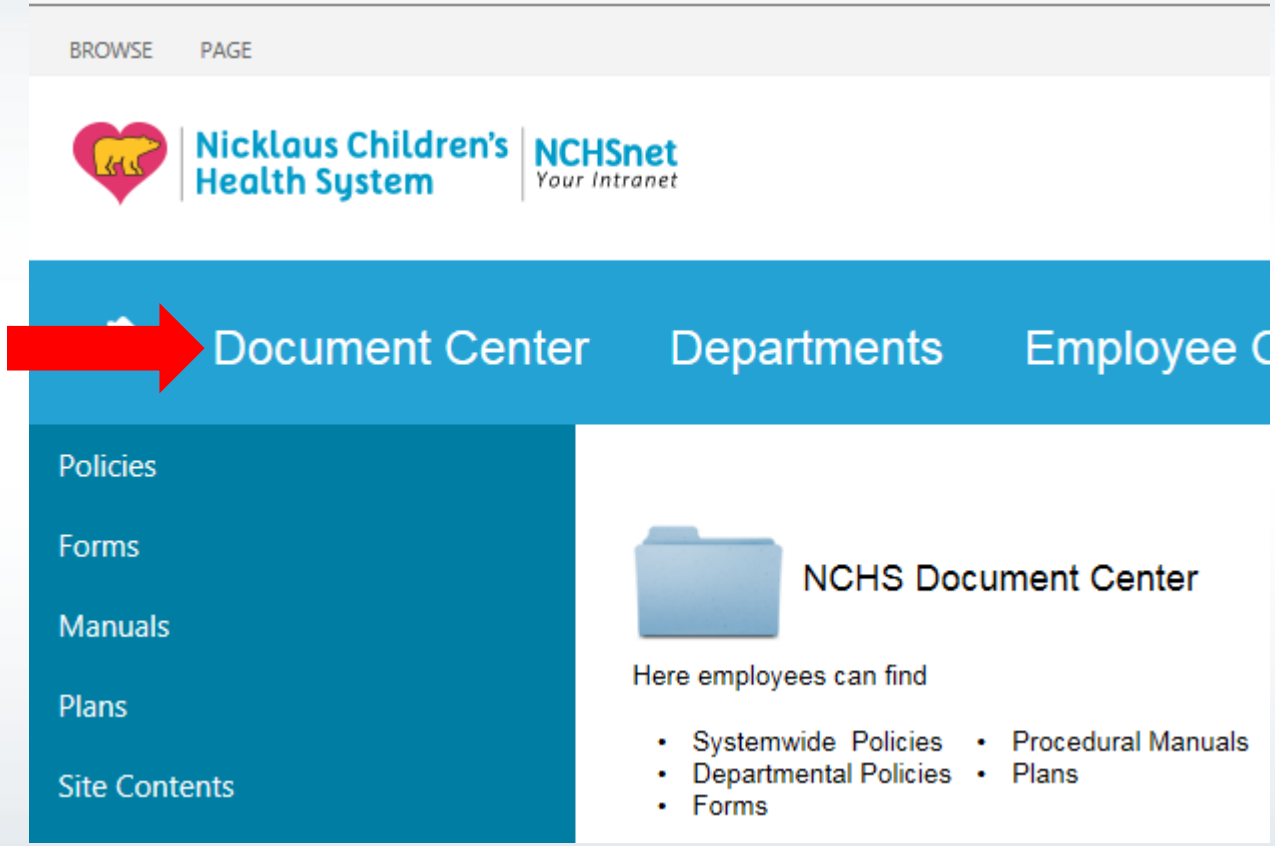
Nicklaus Children's Hospital & Research Institute Policies





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Case Study # 3

- Dr. Peptic wants to conduct research on interventions for IBD in patients at the UMC.
- She requests coded data from a UMC IBD Database which tracks private identifiable healthcare information about living UMC IBD patients.
- The Database Administrator will provide “coded” data.
- Dr. Peptic can readily ascertain the identity of patients.
- She will pull additional patient data from Cerner to correlate the results for her study.

Is this Human Subjects Research?

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Case Study # 3: Q & A

Does the research involve an intervention or interaction with the individuals?

- No interventions or interactions with individuals are described

Does the research involve obtaining information about living individuals?

- Yes - data pertains to living individuals

Is the information private?

- Yes. A patient can reasonably expect that healthcare data will not be made public

Is the information individually identifiable?

- Yes. Dr. Peptic can readily ascertain the identity of subjects based on the data set

Is the activity research involving human subjects?

- Yes. Dr. Peptic is obtaining individually identifiable private information about living individuals

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Key Questions - In Order

Answer questions in proper sequence when considering whether an activity is research, human subjects research, or exempt:

1. Is this project **research**?
2. If so, does it involve **human subjects**?
3. If so, is it **exempt**?

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What Does Exempt Mean?

A federal designation for research activities in which the only involvement of human subjects will be in one or more of the categories outlined in 45 CFR 46.104(d).

Means that the research may be exempt from the requirements of the federal Common Rule (Title 45 CFR part 46) i.e. that the research is **exempt from IRB review**, both initial and continuing IRB review.

- Research with prisoners may not be exempt, except for research aimed at involving a broader subject population that only incidentally includes prisoners.
- Only some exempt categories apply to children
- FDA regulated research is not exempt

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	Exempt Categories	Revisions to Exempt Categories (Jan. 2019 – Common Rule Revisions)
Category 1	Research in Established or Commonly Accepted Educational Settings	Revised to include a condition that the research is not likely to have adverse impacts on students learning required educational content or assessment of educators who provide Instruction
Category 2	Educational Tests, Surveys, Interviews, Observations of Public Behavior	Revised
Category 3	Benign Behavioral Interventions in Conjunction with the Collection of Information From **Adult** Subjects	New Exemption which replaced the pre-2018 Exemption Category (which was eliminated) at this number. **Only applicable for research with adults.**
Category 4	Secondary Research for Which Consent is Not Required	Revised
Category 5	Research and Demonstration Projects that Are Conducted or Supported by a Federal Department or Agency	Revised
Category 6	Taste and Food Quality Evaluation and Consumer Acceptance Studies	Unchanged
Category 7	Storage or Maintenance for Secondary Use for Which Broad Consent is Required	New - not available at Nicklaus Children's Hospital
Category 8	Secondary Research for Which Broad Consent is Required	New - not available at Nicklaus Children's Hospital

Exempt Category 1 – Research Conducted in Established & Commonly Accepted Educational Settings

- Specifically involves normal educational practices
  - Not likely to adversely impact students' opportunity to learn required educational content **or**
  - Not likely to adversely impact the assessment of educators who provide instruction
- This includes:
  - most research on regular and special education instructional strategies and
  - research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

CITI Program “Final Rule Resources” 2018 and CITI course “Overview of Final Rule Revisions” 2019 .

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Exempt Category 2 – Educational Tests, Surveys, Interviews, Observations of Public Behavior

- Now includes visual and auditory recordings as research methods
- Has to meet one of three criteria
  - Information obtained is not identifiable **or**
  - Disclosure outside of the research would not put subjects at risk of harm **or**
  - The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, **and** an IRB conducts a limited IRB review
- ***Participation of children does not qualify if the research involves***:
  - surveys,
  - interviews or
  - the investigator is participating in the activities being observed

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Exempt Category 3 – Benign Behavioral Interventions

- New category and **only applicable for research with adults**.
- Defined as ***brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects***, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing.
- Permitted if one of the following criteria is met:
  - Information obtained is recorded in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
  - Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
  - Information obtained is recorded in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review
- Deception is allowed if subjects are made aware that the research involves deception.

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Exempt Category 4 – Secondary Research

- Covers secondary research uses of identifiable private information or identifiable biospecimens.
- Data no longer need to be existing at the time of the research study as was previously required.
- Allowable if at least one of the following criteria is met:

  (i) The identifiable private information or identifiable biospecimens are publicly available;

  (ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;

  (iii) The research involves only information collection and analysis involving the investigator's use of identifiable health information if:

  - subjects being studied have previously provided HIPAA authorization for future uses or
  - A waiver of HIPAA authorization is approved by the IRB or HIPAA Privacy Board

  (iv) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities

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Implications – Why does it matter and Who decides?

Human Subjects Research:

NCHRI must review the activity, as per Nicklaus Children's Health System **policy** (Review of Research at Nicklaus Children's Hospital, http://policies/dotNet/documents/?docid=16888) and per our accreditation as a Human Research Protection Program (HRPP).

Exempt Human Subjects Research:

NCHRI may provide a Determination of Exemption from IRB review as an established HRPP. Investigators may **not** make this determination themselves, as per NCHS policy (Review of Human Subjects Research that is Exempt from IRB Review, http://policies/dotNet/documents/?docid=17044)

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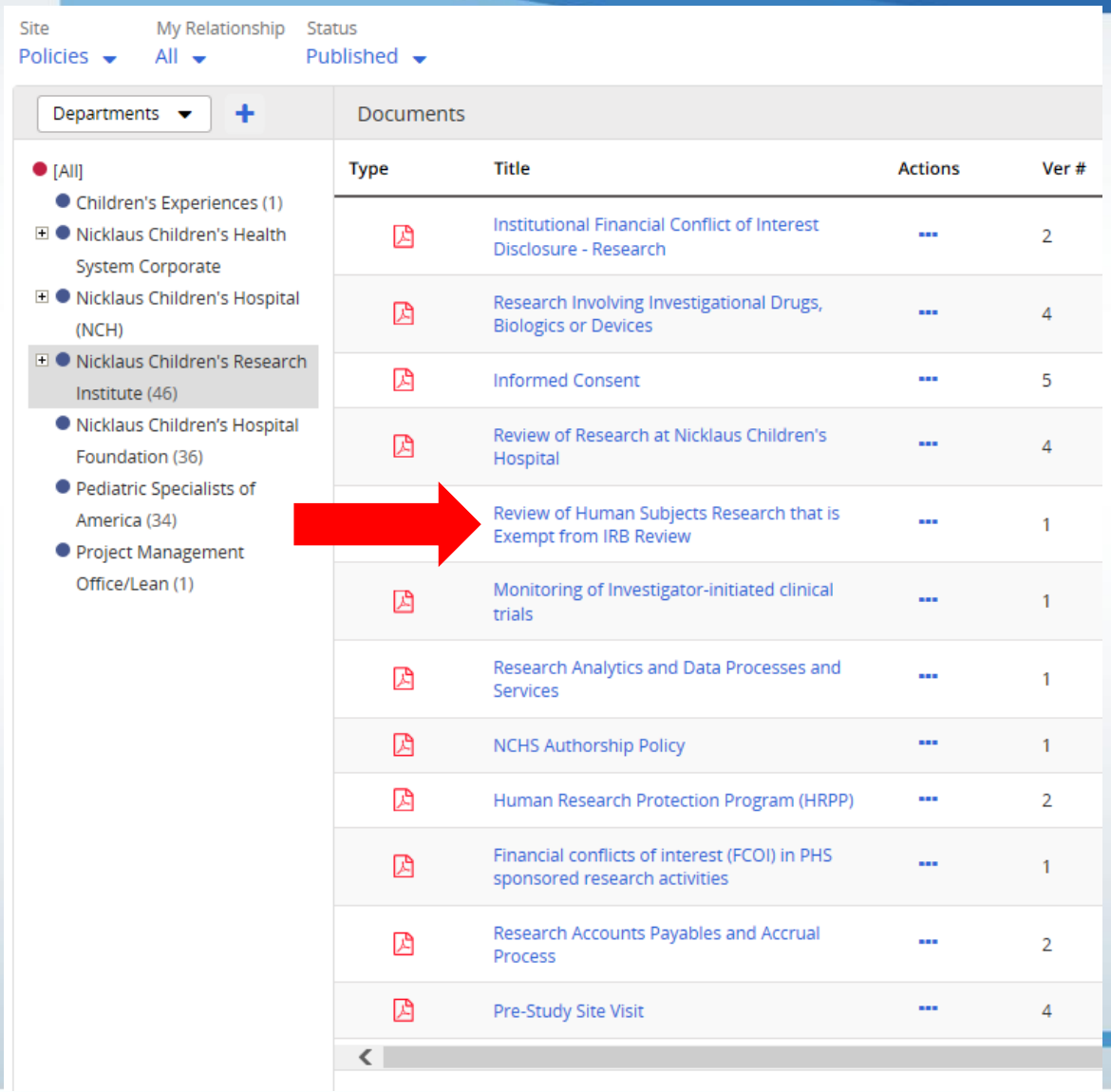

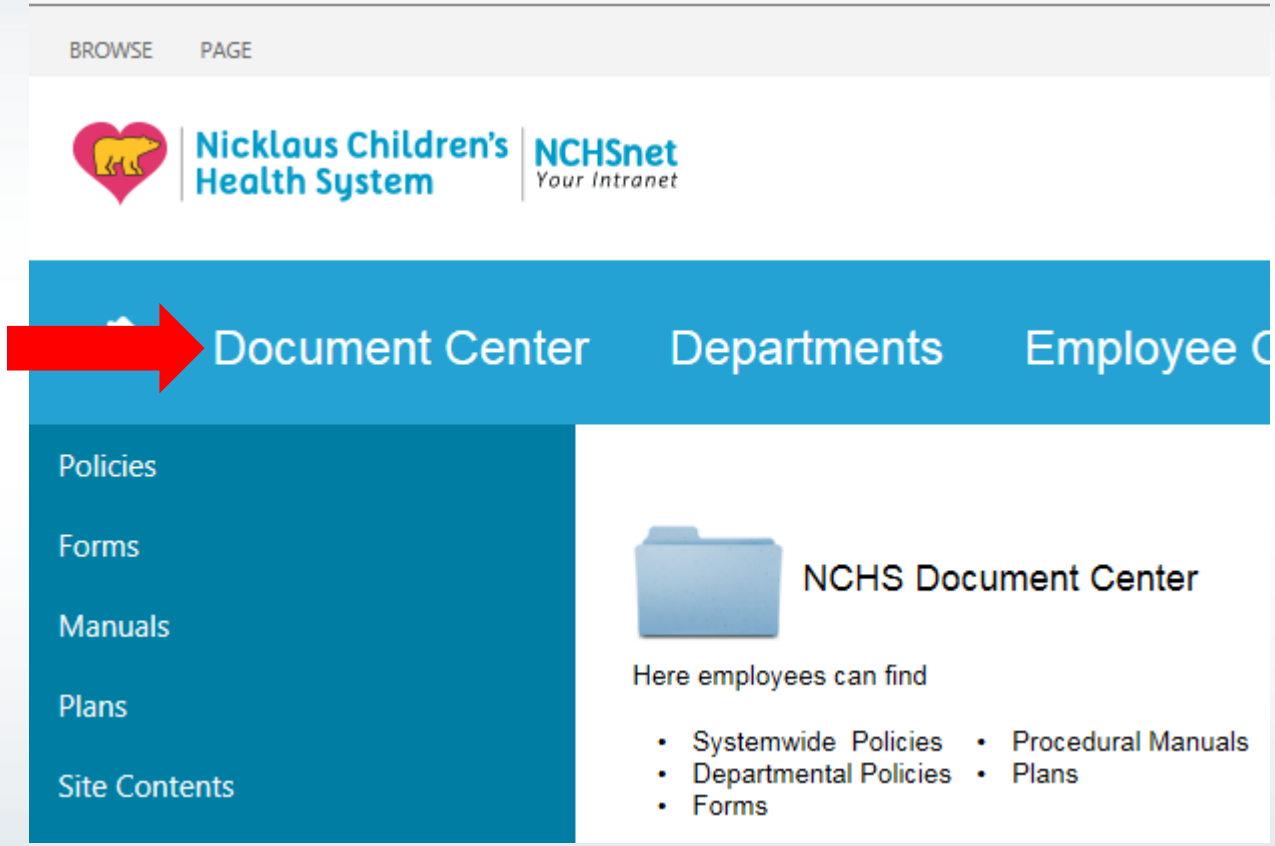

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Case Study # 4

- Dr. Swerlo wants to conduct human research on osteosarcoma.
- He will use patient identifiers to cross reference imaging studies, lab reports, and medical records.
- All of the materials are existing at the time of the proposal and will be borrowed from other areas.
- He will record data in a spreadsheet in such a manner that subjects cannot be identified.
- He returns all materials to the archives.
- No one will be able identify patients by looking at the spreadsheet, including Dr. Swerlo.

Is this Exempt Human Subjects Research?

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Case Study # 4: Q & A

Is this activity eligible for an exemption?

- Yes
- Research involves the study of existing records
- Information is recorded by the investigator in such a manner that subjects cannot be identified

If yes, under which category should be documented?

- Exemption category # 4
- Existing data, documents, records, pathologic specimens, or diagnostic specimens (if publicly available, or recorded by investigator so participants cannot be identified)

If Dr. Swerlo wanted to keep certain PHI elements in his research dataset what additional regulatory approval would be required?

- Waiver of HIPAA authorization, provided by a Privacy Board.

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A word about amendments or… the Devil is in the details…

Amendments (changes) to exempt studies **must** be submitted to NCHRI for review

Why?

Overlooking or changing one detail of the protocol could change the determination…

- From research to human subjects research
- From exempt from IRB review to requiring expedited or limited IRB review

All details of the project must be taken into consideration before these determinations can be made

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Summary – Key Questions

Answer questions in proper sequence when considering whether an activity is research, human subjects research, or exempt:

1. Is this project **research**?
2. If so, does it involve **human subjects**?
3. If so, is it **exempt**?

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What type of study to choose?

- QI projects
- Case report (3 or less cases)
- Observational Study
  - Chart review
  - Outcomes study
  - Surveys
- Interventional Study / Clinical Trial
  - New drug, device, intervention

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Quality Improvement projects

- QI projects
  - ❖ QI activities that are designed solely for internal program evaluation purposes, with no external application or generalization, usually do not constitute human subject research and usually do not require IRB review.
  - ❖ QI activities constitute human subject research and require IRB review, when they are designed or intended, at least in part, to develop or contribute to generalizable knowledge

Use QI or Research Worksheet

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Research vs. QI

	Human Subjects Research	Quality Improvement
Purpose	designed to develop or contribute to **generalizable knowledge**	designed to implement knowledge, assess a process or program as judged by established standards
Starting Point	knowledge-seeking is independent of routine care and intended to answer a question or test a hypothesis	knowledge-seeking is integral to ongoing management system for delivering health care
Design	No protocol changes	adaptive, iterative design
Benefits	might or might not benefit current subjects; intended to benefit future patients	directly benefits a process, system or program; might or might not benefit patients
Risk	may put subjects at risk	does not increase risk to patients (except for privacy or confidentiality of data)
Obligation	no obligation of individuals to participate	participation as component of care
Endpoints	answer a research question	improve a program, process or system
Analysis	statistically prove or disprove hypothesis	compare program, process or system to established standards
Adoption	little urgency to disseminate results quickly	rapid adoption into local care delivery
Presentation	obliged to share results	encouraged to share insights

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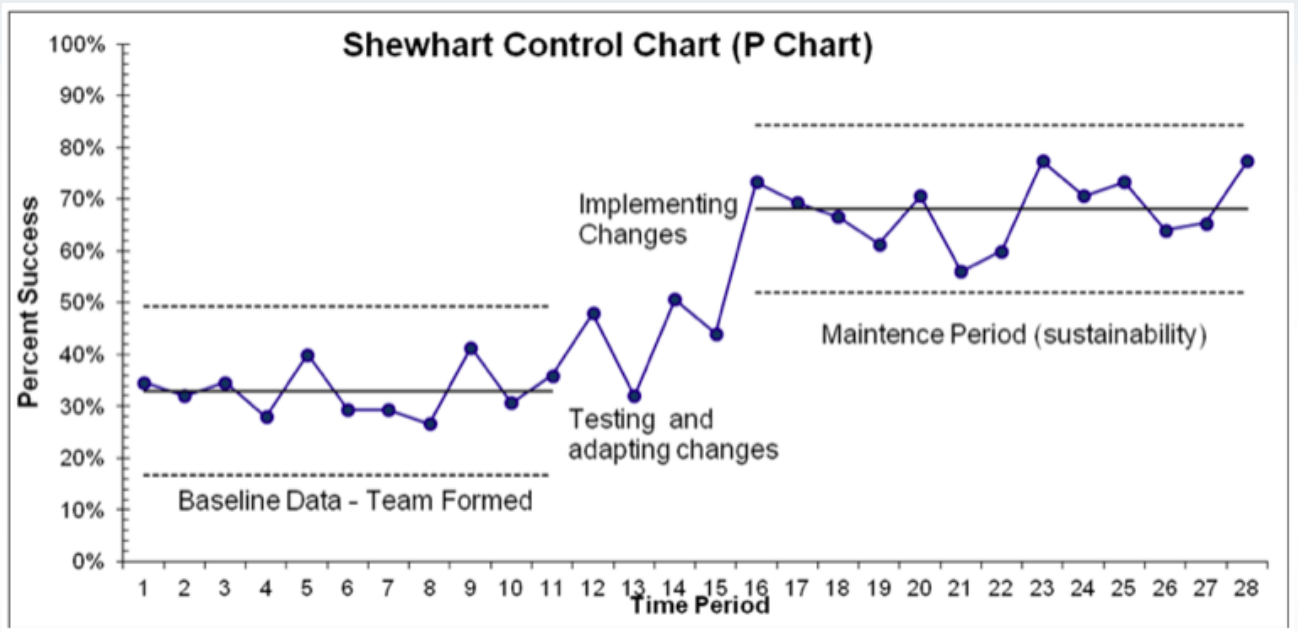
Outcomes for QI

- Length of stay (LOS)
- Mortality, morbidity
- Waiting time
- Simple questionnaire on satisfaction, pain scale, experience etc.



Interventions for QI

- Process or workflow improvement
- Using new standard of care procedure (not investigational)

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Do I need a project plan/protocol for QI?

- Are you planning to publish in a peer-reviewed journal or present at a conference?
- Coming soon – a NCHS application to conduct a QI project, which will require a QI project plan/protocol.

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Resources

- Portal at the Research Institute site
- (https://intranet.mch.com/EN/Departments/cr/pages/home.aspx):
  - Research Consultation Request form
  - ProtocolBuilder™
  - eApplication to Conduct Research
  - List of HIPAA identifiers
  - QI or Research Worksheet
  - ICF templates
  - And more…

- Email Contacts:
  - ClinicalResearch@NicklausHealth.org
  - RAD@NicklausHealth.org
  - RegulatoryAffairs@NicklausHealth.org

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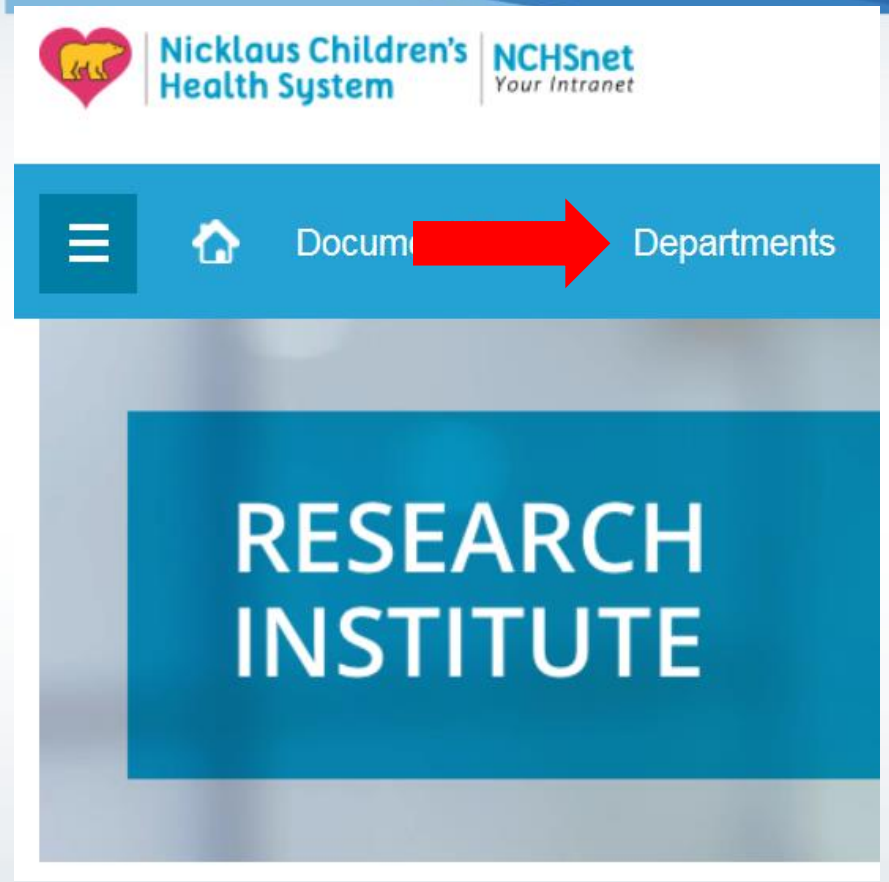
Resources for Research Investigators at Nicklaus Children's Hospital



Email Contacts:

- RAD@NicklausHealth.org
- RegulatoryAffairs@NicklausHealth.org

Investigator's Resources

- Research Consultation Request Form
- Protocol Builder
- eApplication to Conduct Research
- HIPAA Identifiers
- Exempt Guidance
- NCH IRB Informed Consent Template
- Delegation of Authority Form
- eSubmission of Reportable Information
- CITI Training for Research
- Federal Regulations for Research
- Research Decision Charts
- FDA Regulations: GCP & Clinical Trials
- ICH GCP Guideline
- AAPOR Guidance for Survey Research
- Quality Improvement Worksheet

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