



Clinical and Translational
Science Institute
at Children's National

A PARTNERSHIP WITH THE GEORGE WASHINGTON UNIVERSITY

KL2-Special Interest Group Event

Bootcamp for New Investigators in Clinical Research

This series of 4, two-hour workshops discusses how to operationalize biologic clinical trials and introduces resources in managing investigator-initiated trials at GW and CNH. There is an emphasis on available programs, templates, and resources.

Review archived Bootcamps [here](#).

For Zoom links and calendar invites, please contact Pesh Rubinstein at

Pesha.Rubinstein@gwu.edu

or

gwsmsresearch@gwu.edu

Session 4. Mastering Event Reporting Thurs, FEB. 16, 12 – 2 PM (virtual)

Adverse Events & Reporting (10 slide max; 15 min each speaker)

12:00-12:15 What is a serious adverse event? - **Bruno Petinaux, MD**

12:15-12:30 Event reporting and the IRB - **Elissa Malkin, DO, MPH**

12:30-12:45 Event reporting in longitudinal studies - **Nickie N. Andescavage, MD**

12:45-12:50 *Break*

Clinical Trial Safety Management (10 slide max; 15 min each speaker)

12:50-1:05 Types of safety management plans and processes - **Robin McGarry, MD**

1:05-1:20 FDA Findings in Clinical Trials - **Adelaide Robb, MD**

1:20-1:35 What data can you use (or not use) from the EHR - **Kristen Breslin, MD**

1:35-1:40 *Break*

1:40-2:00 Breakouts: Institutional Solutions to Challenges: Lessons Learned (20 min breakout; 2 facilitators per session)

Emails and discoverability? Who keeps consent forms – paper, “e”, and hybrid?

When to involve the IRB? Pharmacovigilance?

GW: Radwa Aly, MSc; Sarah Ford-Trowell, MPA

CNH: Kristen Breslin, MD; Caitlin Joffe, MBA, CCRP; Marissa Horrigan, PharmD

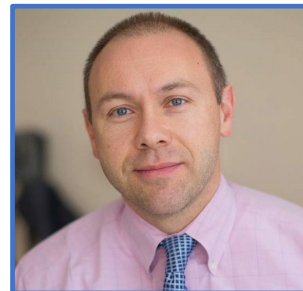
DETAILED AGENDA

ADVERSE EVENTS & REPORTING

12:00-12:15 What is a serious adverse event?

Bruno Petinaux, MD · Email: Bruno.Petinaux@gwu-hospital.com

Bruno Petinaux, MD, was appointed Chief Medical Officer (CMO) at the George Washington University Hospital in June 2017. Prior to his official appointment, he served as Interim CMO for a year, during which he led the development and execution of many safety and quality initiatives. In addition to his role as CMO, Dr. Petinaux is an associate professor in the Department of Emergency Medicine at the GW School of Medicine and Health Sciences and has been an emergency medicine physician at GW Hospital since 2002. He co-chairs GW Hospital's Emergency Management Program and is the Emergency Management Track Director for the GW School of Medicine and Health Sciences. Along with his work at GW, Dr. Petinaux supports our community as a medical team manager for the Virginia Task Force 1/USA 1 Urban Search and Rescue Team.



12:15-12:30 Event reporting and the IRB:

Elissa Malkin, DO, MPH · Email: emalkin@email.gwu.edu

Elissa Malkin DO, MPH, is Associate Research Professor of Medicine at the GW School of Medicine and Health Sciences. She is a core member of GW's Vaccine Research Unit. She is also a member of the GW Institutional Review Board. She completed residencies in both Family Medicine and Preventive Medicine. She has over 20 years of experience in clinical research with a focus on vaccine development. She has held positions at the National Institutes of Health, PATH's Malaria Vaccine Initiative and in the pharmaceutical industry prior to GW. She has 10 years of experience in the pharmaceutical industry in both clinical development and pharmacovigilance.



12:30-12:45 Event reporting in longitudinal studies:

Nickie N. Andescavage, MD · Email: nniforat@childrensnational.org

Nickie Andescavage, MD, is clinical director of the Developing Brain Institute (DBI) at Children's National Hospital. In this role she supports coordination of DBI's prenatal and NICU studies, leads engagement efforts with obstetricians and maternal-fetal medicine specialists, and expands our clinical research enterprise to a growing number of community NICUs. She is also an attending physician in the Division of Neonatal-Perinatal Medicine at CNH; director of the Perinatal-Neonatal Program for the Prenatal Pediatrics Institute; and a tenure-track Assistant Professor of Pediatrics at the GWU School of Medicine & Health Sciences. She is the Principal Investigator of an active Eunice Kennedy Shriver National Institute of Child Health and Human Development K23 career development grant, recipient of the District of Columbia Center for AIDS Research Pilot Award on advanced placental imaging in pregnant women living with HIV and a Co-Investigator on several research studies on mechanisms of acquired brain injury in the neonatal population.



12:45-12:50 Break

CLINICAL TRIAL SAFETY MANAGEMENT

12:50-1:05 Types of safety management plans and processes:

Robin McGarry, MD · Email: robinjmcgarry@email.gwu.edu

Robin McGarry, MD, is Adjunct Associate Professor of Clinical Research and Leadership at the GWU School of Medicine and Health Sciences and teaches a master's level course, Clinical Research for Regulatory Affairs. She is a board-certified internist and nephrologist with over 35 years of experience in the pharmaceutical industry. She has held positions in both large and small pharmaceutical companies including Astellas, Pfizer, Ciba-Geigy Corp. (now Novartis), and ICI Pharmaceuticals (now Astra-Zeneca). These positions included senior leadership/functional and line management of global pharmacovigilance organizations, medical affairs and clinical development groups. Dr. McGarry currently provides clinical and regulatory strategic consulting services to the pharmaceutical industry.



1:05-1:20 FDA Findings in Clinical Trials

Adelaide Robb, MD · Email: AROBB@childrensnational.org

Adelaide Robb, MD, is a psychopharmacologist with ongoing research studies in depression and mood disorders, anxiety and attention deficit disorder. She is Chief of the Division of Psychiatry and Behavioral Sciences. Dr. Robb, who trained at Johns Hopkins University and the National Institutes of Health, has been on the medical staff in the Division of Psychiatry and Behavioral Medicine at CNH since 1996, rising to the rank of Professor (with tenure). She is an internationally known clinical researcher and has participated in and led multiple therapeutic trials for children with a variety of behavioral and psychiatric conditions.



1:20-1:35 What data can you use (or not use) from the EHR:

Kristen Breslin, MD, MPH · Email: kbreslin@childrensnational.org

Kristen Breslin, MD, MPH, is a pediatric emergency medicine physician at Children's National Hospital. She earned her MD degree at Harvard Medical School and completed her pediatric emergency medicine fellowship at Children's National. She is the Research Director of the Pediatric Emergency Medicine Fellowship and Assistant Director of Research for the Division of Emergency Medicine, and Chair of the CNH Institutional Review Board. She is also a Global Health Faculty Mentor for pediatric residents at Children's.



1:35-1:40 *Break*

1:40-2:00 Breakouts: Institutional Solutions to Challenges: Lessons Learned *(20 min breakout; 2 facilitators per session)*

Breakout questions:

*Emails and discoverability? Who keeps consent forms – paper, “e”, and hybrid?
When to involve the IRB? Pharmacovigilance?*

GW Breakout: Radwa Aly, MSc; Sarah Ford-Trowell, MPA

Radwa Aly, MSc has over 14 years of extensive experience in clinical research, especially in behavioral health and neurosciences. She is GW Senior Director of Clinical Research Operations. She is currently pursuing a PhD in Translational Health Sciences at the George Washington University School of Medicine and Health Sciences. Email: raly@mfa.gwu.edu



Sarah Ford-Trowell, MPH, is the Senior Manager of Regulatory and Compliance in the George Washington Office of Clinical Research (GW OCR). She and the OCR are a resource for faculty and staff involved in clinical and translational research. The OCR is committed to providing clinical research education and ensures that operations, regulatory-compliance, and finances are properly managed. Email: sstocker@mfa.gwu.edu



CNH Breakout: Kristen Breslin, Caitlin Joffe; Marissa Horrigan

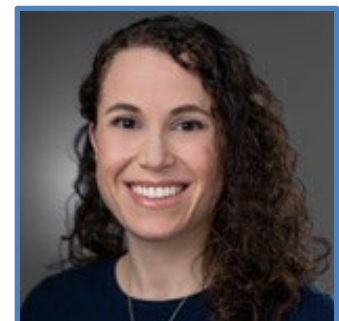
Kristen Breslin, MD, MPH, is a pediatric emergency medicine physician at Children's National Hospital. She earned her MD degree at Harvard Medical School and completed her pediatric emergency medicine fellowship at Children's National. She is the Research Director of the Pediatric Emergency Medicine Fellowship and Assistant Director of Research for the Division of Emergency Medicine, and Chair of the CNH Institutional Review Board. She is also a Global Health Faculty Mentor for pediatric residents at Children's. Email: kbreslin@childrensnational.org



Caitlin Joffe, MBA, CCRP, has over 15 years' experience working in various positions in clinical research with a focus on oncology studies, having overseen everything from quality assurance and study compliance to staffing and budgeting of multisite institutional trials. She is an experienced trainer, educating new colleagues both domestically and abroad. She joined CNH in January 2022 from the Cancer Center at Johns Hopkins and currently serves as Director of Research Quality Assurance. Email: CJOFFE@childrensnational.org



Marissa Horrigan, PharmD, is the Investigational Drug Services Manager with CNH. Before that she was on the West Coast at Cedars-Sinai and the San Francisco Veterans Affairs Medical Center. She participated in hospital Institutional Review Boards for the past 8 years and has worked with both adult and pediatric investigational studies, including oncology, cellular products, viral vectors, and gene therapy. Email: mhorrigan@childrensnational.org



Resources

Note: After general resources, you will find some resources specific to CNH or GW. Be sure to review the resources specific to your institution provided by speakers.

Definitions, from FDA:

What is an Adverse Event? US Food & Drug Administration [here](#):

An adverse event is any undesirable experience associated with the use of a medical product in a patient. The event is serious and should be reported to FDA when the patient outcome is:

Death

Report if you suspect that the death was an outcome of the adverse event, and include the date if known.

Life-threatening

Report if suspected that the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.

Hospitalization (initial or prolonged)

Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event.

Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

Disability or Permanent Damage

Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

Congenital Anomaly/Birth Defect

Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

Required Intervention to Prevent Permanent Impairment or Damage (Devices)

Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.

Other Serious (Important Medical Events)

Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

The Joint Commission Sentinel Event Policy and Procedures [here](#)

Identify death/ permanent harm/ severe temporary harm & intervention required to sustain life as sentinel events. Each accredited organization is strongly encouraged, but not required, to report sentinel events to The Joint Commission.

Advarra has several articles about reporting adverse events:

- **Reporting to the IRB: Serious Adverse Events (SAEs) in Drug Studies [here](#)**
- **Reporting to the IRB: What NOT to Report [here](#)**
- **Reporting to the IRB: Unanticipated Device Effects (UADEs) in Medical Device Studies [here](#)**

Bowman MA, Maxwell RA. A beginner's guide to avoiding Protected Health Information (PHI) issues in clinical research - With how-to's in REDCap Data Management Software. J Biomed Inform. 2018;85:49-55.
doi:10.1016/j.jbi.2018.07.008 [\[Article\]](#)

FDA. Adverse Event Reporting to IRBs — Improving Human Subject Protection [HERE](#)

FDA. Safety Reporting Requirements for INDs (Investigational New Drug Applications) and BA/BE (Bioavailability/Bioequivalence) Studies [HERE](#)

FDA Draft Guidance (updated 2021): Investigator Responsibilities – Safety Reporting for Investigational Drugs and Devices [FDA Guidance IND Reporting 2021](#)

FDA. Regulations: Good Clinical Practice and Clinical Trials [HERE](#)

HHS.gov. Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events: OHRP Guidance (2007). [HERE](#) [Note “[Appendix A: Glossary for Key Terms](#)”]

NCI GUIDELINES FOR INVESTIGATORS: ADVERSE EVENT REPORTING REQUIREMENTS FOR DCTD (CTEP AND CIP) AND DCP INDs AND IDEs. [HERE](#) or at HHS.gov [Guidance Portal](#)

NIAID Safety Monitoring Plan [HERE](#)

NIH registration portal for “Introduction to the Principles and Practice of Clinical Research (IPPCR) [HERE](#)
NIH IPPCR individual lecture videocasts [HERE](#) – particularly:

- IPPCR: Clinical Trial Registration and Results Reporting (Zarin)
- IPPCR: The Clinical Researcher & the Media (Burklow)

Resources specific to Children’s National Hospital (CNH sign-in required):

Children’s National: “Events and Information Requiring Reporting to the IRB” **at end of lookbook Resources – note especially:**

Decision Chart 1: Adverse Events and Decision Chart

Chart 2: Non-AE Unanticipated Problems and Protocol Deviations

IRB sharepoint homepage: [HERE](#)

[LINK](#) to reporting events to CNH IRB on IRBear

Reporting Events Policy also available in the CNH policy portal under “Events and Information Requiring Reporting to the IRB”

Transmission and Storage of Identifiable Health Information at CNH – [Policy Portal](#)

Appropriate use of faxing and email for messages containing health information at Children’s National – search the policy portal for “Appropriate Use of Information Resources”, listed under IT Security. Also recommended under IT Security is the “Cloud Data Storage Standard.”

Reporting Clinical Safety Events at CNH (research or non-research)

- [Safety Event Reporting System](#)
- [Policy Portal](#)
 - “Medication Errors, Adverse Drug Events (ADE), and Adverse Drug Reactions (ADR)” under Healthcare Professionals

Resources specific to George Washington University:

GWU ACRP Sign-up [here](#); note:

- ACRP Developing Protocols & Manuals of Operating Procedures
- ACRP Risk-based Monitoring Essentials
- ACRP [Recommended Curriculum for Clinical Research Training](#), emphasizing Good Clinical Practice

GWU IRB website: <https://humanresearch.gwu.edu>

GW Hospital Research Policy:

Policy Title:	Research Policy		
Location:	GWUH	Department:	Medical Staff
Policy Number:		Current Review Date:	
Original Effective Date:	December 2022	Current Effective Date:	

I. Purpose:

To establish processes for all clinical research at the George Washington University Hospital (GWUH).

II. Policy:

It is the mission of the George Washington University Hospital to foster clinical research and education. In the pursuit of knowledge, the Staff, House Staff, and Medical Staff at GWUH may initiate clinical research with the intent of publishing the work. This policy governs all aspects of an Institutional Review Board approved study within GWUH.

III. Definition:

- Research – scientific/medical detailed study of a subject in order to discover new information or new understandings
- Institutional Review Board (IRB) – committee that has been formally designated to review and monitor biomedical research involving human subjects in accordance with FDA regulations.
- Principal Investigator (PI) – person responsible for the research activity, clinical trial, or grant
- Co-Investigator – designated person assisting the Principal Investigator in the conduct of research
- Industry Sponsored Research – research paid for by an industry organization that has contracted with a PI to conduct a clinical trial that involves an intervention with, or observation of, a disease or biomedical condition, or a registry/repository related to a disease or biomedical condition.
- Privacy Officer – designated healthcare administrator responsible for safeguarding patient confidentiality at GW Hospital
- Office of Clinical Research – GW School of Medicine and Health Sciences office that has broad responsibility and oversight for the administration and regulatory oversight and management of clinical research at GW and its clinical partners, the GW MFA and the GW University Hospital.
- Office of Sponsored Research – George Washington University School of Medicine and Health Sciences office responsible for federal/foundational funded research administration

IV. Procedure for all non-exempt and exempt studies:

- The Principal Investigator and/or designee forwards all applications to GWUH Chief Medical Officer or their designee
 - GW IRB studies
 - GW IRB application and relevant information
 - Western IRB studies

1. Hospital questions for sponsored research
 2. Study Protocol
 3. Study Contract
 4. Study Budget/Approved Quote
- b. Each application undergoes a review by the relevant GWUH Administrator as determined by the CMO such as
- i. Privacy Officer
 - ii. Information Security
 - iii. Data Management
 - iv. Clinical
 1. Chief Medical Officer (CMO) and/or Chief Nursing Officer (CNO)
 2. Relevant Department Director
 - a. Nursing
 - b. Laboratory
 - c. Radiology
 - d. Pharmacy
 - e. Rehabilitation
 - f. Health Technology Management
 - v. Finance
 - vi. Contracting (for contractual review prior to execution for industry sponsored research)
- c. Once approved, the relevant GW Hospital administrator notifies the PI of the approval of the study at GW Hospital.
- d. The PI is responsible to ensure that all study related activities are charged to the appropriate Research Cost Center and not the patient's medical insurance carrier.
- i. GWUH will invoice the PI for study related costs within 30 days of patient discharge
 - ii. The PI agrees to reimburse GWUH for study related costs per the pre agreed upon fee schedule within 90 days.
 - iii. GWUH will periodically audit patient's billing records to ensure compliance
- e. The PI is responsible for all study related audits. GWUH will provide hospital related data relevant to the audit as requested and collaborate with all regulatory bodies as necessary.

V. Study Life Cycle

- a. The PI and/or designee is responsible for identifying, enrolling, and consenting the patient in the study. No study medications can be administered without an informed consent, unless the IRB has approved an exemption for informed consent.
- b. The PI and/or designee is responsible for all training, education, competencies, documentation, reporting, and auditing of research studies.
- c. The PI must notify the CMO of any privacy, information security, protocol violations or clinical complications within 24 hours.
- d. The PI must notify the CMO of study participants who withdraw their consent while participating in a study while hospitalized at GW Hospital.
- e. The PI must notify the involved departments and CMO of the conclusion of enrollment and/or data collection of a study via email.

VI. Study Medications

- a. The PI will engage with the GWUH Pharmacy, Nursing and/or Medical Staff regarding study medications and collaborate with the IDS pharmacy.
 - i. All study medications administered at GW Hospital will be processed through the GWUH Pharmacy
 1. Storage control requirements
 2. Inventory control
 3. Bar coding of the medication
 - a. For non formulary medications, the pharmacy will enter a non formulary order in CERNER for medication administration with the order comment
 - i. ** Investigational Study Drug **
 4. return of any study medications to the PI or designee or individual as dictated by the study protocol at the conclusion of the study
 - ii. Determine whether or not the medication will be prepared at the GWUH Pharmacy

1. Compounding
 2. Mixing
 3. Note that for certain studies, GWUH Pharmacy may be asked on behalf of the IDS pharmacy only for the preparation of the medication to be used by the PI at a site other than GWUH
- b. The PI and/or designee is responsible to ensure and document that GWUH Pharmacy and Nursing staff and primary medical team caring for the patient have all the relevant training, supplies, competencies, and knowledge to safely prepare and administer the study medication
 - c. The protocol and all drug information must be available in the pharmacy.
 - d. The protocol, consent, and study team 24/7 contact information must be included in the patient's paper chart.
 - e. The PI and/or designee is responsible that the study enrollment be noted on the patient's white board.
 - f. The pharmacy is responsible for entering a flag into the patient's medical record.
 - g. The patient must be enrolled in Powertrials with research information available in the patient's electronic medical record.
 - h. The charge nurse is responsible for including the study enrollment during charge nurse hand off and in the daily huddle.
 - i. The PI and/or designee is responsible to ensure that all treatment teams caring for the patient are knowledgeable in regards to the study medication, side effects, contraindications, and complications.
 - i. The PI must place a study drug fact sheet into the medical record
 - j. The PI and/or designee is responsible for determining the study drug administration schedule according to the protocol and relaying this information to GW Pharmacy, nursing staff and medical team
 - k. The individual administering the study medication must ensure that the consent is in the medical record and that they have been trained on the administration of the study medication

VII. Radioactive studies

- a. This policy does not apply to radiopharmaceutical or radioactive studies. These will need to go through the Radiation Safety Officer.

VIII. Study Laboratory Specimen

- a. Study related laboratory specimens will be processed in the usual fashion at GWUH for laboratory tests currently being processed by GWUH (note the exception of the billing) upon agreement by the nursing and laboratory leadership.
 - i. The PI and/or designee may, as part of the study, obtain a laboratory specimen themselves.
 1. The PI is responsible that they and/or their designee is fully trained and approved to obtain specimens at GWUH
 2. The PI is responsible for the ordering, collecting, processing, shipping, handling, tracking, and reporting of the specimen.
- b. The PI is responsible to ensure that the GWUH personnel obtaining and processing the specimens are knowledgeable of the study if not part of a standard laboratory test being done at GWUH.
- c. The PI must determine critical value levels of GWUH performed laboratory test results. The PI must be available at all times for notification purposes of such critical value reports by the laboratory, in addition to the primary team being notified.
- d. The PI must develop a process with the laboratory to order laboratory tests not typically performed at GWUH.
 - i. The PI must ensure that the ordering, collecting, processing, shipping, handling, tracking, and reporting process of such laboratories be clearly determined.
- e. The PI must determine how long the laboratory will maintain specimens ordered as part of the study.
- f. The PI is responsible for coordinating with the laboratory regarding any 'send out' specimens to ensure proper labeling, transportation, and delivery in accordance with all rules and regulations.

IX. Radiology and Cardiology Studies

- a. The PI is responsible to work with the respective Director as part of the study approval process to address radiology and/or cardiology related study components
- b. GWUH staff will perform standard studies already performed at GWUH in a standard fashion if agreed upon. GWUH staff will not be able to perform any diagnostic study not already being done at GWUH unless all necessary training, education, and supervision has been obtained.
- c. GWUH will not utilize any non FDA approved product unless approved under a IND/IDE.
- d. The PI and/or designee is responsible for the interpretation and reporting of the performed study.

X. Scheduling of Procedures and Payment

- a. GW Hospital's Finance Department will determine the Charge Master annually for all commonly used procedures and charge codes. The Charge Master will have a cost escalation over the next 5 years to account for cost increases over the lifetime of a study. This charge master will govern the study related costs at GW Hospital.
- b. The PI and/or designee will reach out to the Central Business Office to schedule any diagnostic procedures including the study number and GW IRB number. The study will be scheduled using Research code 931 when the CBO registers the patient for the study, adding the study number and GW IRB number in the insurance ID field.
- c. The GW Hospital Business Director runs a quarterly report by code 931 and study number and/or GW IRB number including the patient's FIN and Charge code.
- d. The GW Hospital Business Director forwards the information to the Office of Research business operations teams for payment.
- e. Three months after invoicing the Research Office, the GW Hospital Business Director will audit the account for payment.
 - i. If late the GW Hospital Business Director will notify the Chief Medical Officer

XI. Study Devices

- a. Only FDA approved study devices will be studied at GWUH unless approved under a IND/IDE.
- b. The PI is responsible to ensure all training and education of the staff regarding any study device not currently in use at GWUH.
- c. Health Technology Management is responsible to check all study devices prior to use.
- d. The PI must ensure that the medical record contains the serial number and device information in the patient's medical record.
- e. The protocol, consent, and study team 24/7 contact information must be included in the patient's paper chart.
- f. The PI and/or designee is responsible that the study enrollment be noted on the patient's white board.
- g. The patient must be enrolled in Powertrials with research information available in the patient's electronic medical record.

XII. Research Team

- a. The PI must be a member of the GWUH Medical Staff or be an employed Staff member.
- b. Employed staff members must have permission by Hospital Administration to participate in a research study as the PI
- c. The PI may have co-investigators on the study which are GWUH affiliated individuals (existing members of the Medical or House Staff or GW SMHS students or GWUH Staff members), who have received the required training
- d. The PI may have unaffiliated individuals as co-investigators who will need to complete the Medical Staff Research Observer documentation and required training.
- e. The PI must adhere to all rules and regulations regarding conflicts of interests.
- f. The PI must ensure that all individuals working on the study are added to the research team in the IRB application and have completed appropriate CITI trainings

XIII. Research related complaints

- a. Should the primary stakeholders (PI or GWUH, sponsor, etc.) become aware of a complaint regarding to research, they should notify the CMO and the CMO will engage the relevant stakeholders to work in addressing the complaint.
- b. GWUH will collaborate with all relevant regulatory bodies in the reporting of any complaint as necessary.

XIV. Emergency Use of an Investigational Drug or Device

- a. Indications
 - i. A patient's condition requires the prompt administration of an investigational drug or use of device which is part of a clinical protocol not approved for use at GW Hospital
- b. The attending physician of the patient must document in the patient's chart the indication, medical decision making, and consent, using a standard procedural consent.
- c. A second attending physician must concur with the attending physician as to the indication for emergency use of an investigational drug or device in the care of the patient and document in the medical record as well.
- d. The Chief Medical Officer must be notified of the use of the investigational drug or device prior to use/administration.
- e. The attending physician must follow all above operational aspects in the use of the drug or device.

APPROVED:

Bruno Petinaux, MD
Chief Medical Officer

Date:



I. POLICY STATEMENT:

A. The Children's National Hospital (Children's National) Human Research Protection Program (HRPP) maintains written procedures to ensure prompt reporting of any unanticipated problems involving risks to subjects or others to the Institutional Review Board (IRB), appropriate institutional officials, and the pertinent Federal Department or Agency head, in keeping with federal regulations 45 CFR 46.108(a)(4)(i) and 21 CFR 56.108(b)(1).

Consequently, investigators are required to promptly report to the IRB any events which:

- Are unexpected;
- Are related or possibly related to participation in the research; **and**
- Place subjects or others at greater risk of physical, psychological, economic, or social harm than previously known or recognized (i.e., indicate new or increased risks to subjects or others)

Federal regulations also require that all changes to an approved protocol must be submitted to the IRB for review and receive approval prior to implementation, unless the change is to eliminate an immediate harm to a research subject (45 CFR 46.103(b)(4); 21 CFR 56.108(a)(4)). Any departure from the protocol that occurs without prior IRB approval and is identified retrospectively is called a deviation and must be reported to the IRB.

In addition to reporting these events to the Children's National IRB, investigators must also comply with FDA, study sponsor/funding agency, and external IRB reporting requirements, as applicable.

B. Definitions and Examples

1. **Adverse Event:** Any untoward medical occurrence involving a research subject and associated with the use of a drug/intervention, whether or not considered drug/intervention related. Most adverse events are expected (anticipated), based on previous clinical experience. These events are described in the Investigator Brochure (IB) or package insert for a drug or biological product. Adverse events described in the research informed consent documents are expected; however, they may be more severe or occur more frequently over the course of a study than anticipated.
2. **Protocol Deviation:** Any action or process that departs from the IRB approved study protocol, involving one incident and identified retrospectively. Protocol deviations are considered to be either serious or non-serious. Examples (not to be considered an all-inclusive list):
 - Omissions of study procedures;

- Use of unapproved recruitment materials;
- Subject signed invalid informed consent form;
- Enrollment of an ineligible subject;
- Over- and under-dosing of study medication;
- Subject visit outside window;
- Improper storage of study drugs and devices;
- Missing or no source documentation (e.g. missing labs, physician notes);
- Addition of study procedures without prior IRB approval

Protocol deviations are classified as either *major/significant* or *minor*, based on both the direct or potential effect of the action or process on the specific subject(s) and the entire subject population, and/or on the overall integrity of the study design and results.

- a) A **Major/Significant Deviation** meets at least one of the following criteria:
- The action or process directly or potentially disrupts the study progress, such that the study design and results would be compromised; or
 - The action compromises the safety and welfare of study subjects.

A **Minor Deviation** meets both of the following criteria:

- The action or process does not disrupt the study progress, such that the study design and results would be compromised; and
- The action does not compromise the safety and welfare of study subjects.

b) Examples of Minor and Major/Significant Deviations

Example 1. Subject Enrolled Did Not Meet Eligibility Criteria

- Minor deviation: N/A
- Major or Significant deviation: A low-birth weight infant was enrolled into a treatment trial for normal weight infants and low weight infants are at higher risk for an adverse event.

Example 2. Invalid Informed Consent Form Signed

- Minor deviation: Subject signs an expired/invalid consent form that has not changed significantly.
- Major or Significant deviation: Subject signs an expired consent form that has since added or deleted study procedures outlined in the new consent form.

Example 3. Visit Outside Study Window

- Minor deviation: Visit outside study window, but has no impact on subject or study; e.g., subject did not miss any necessary follow-up exams, or delay vital treatments (drug or behavioral).
- Major or Significant deviation: Visit significantly outside study window, such that subject was placed at risk due to delayed follow-up, and/or study results compromised due to lost results.

Example 4. Informed Consent Form

- Minor deviation: Subject/Guardian did not receive a copy of the signed consent form. Upon discovery, a copy is given to the subject at the next

- visit, or mailed if the subject has since completed the study.
 - **Major or Significant deviation:** Subject was enrolled without subject/guardian signing an informed consent form. Upon discovery of such a case, the subject should immediately be consented and the IRB notified promptly.
3. **Serious Adverse Event (SAE):** An event that involves a research subject and results in any one of the following:
- *Death* - When it is suspected as being a direct outcome of the adverse event and not due to disease progression.
 - *Life Threatening Situation* - When the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death.
 - Examples: Pacemaker failure; gastrointestinal hemorrhage; bone marrow suppression; infusion pump failure that permits uncontrolled free flow resulting in excessive drug dosing.
 - *Hospitalizations (initial or prolonged)* - When admission to the hospital or prolongation of a hospital stay results because of the adverse event.
 - Examples: Anaphylaxis; pseudo membranous colitis; bleeding that causes or prolongs hospitalization; need for upgraded hospital care, as when a hospitalized subject is transferred to the ICU.
 - *Disability* - When the adverse event resulted in a significant, persistent, or permanent change, impairment, damage, or disruption in the patient's body function/structure, physical activities, or quality of life.
 - Examples: Cerebrovascular accident due to drug-induced hypercoagulability; toxicity; peripheral neuropathy.
 - *Congenital Anomaly* - When it is known or suspected that exposure to a medical product prior to conception or during pregnancy resulted in an adverse outcome in the child.
 - Examples: Vaginal cancer in female offspring from diethylstilbestrol during pregnancy; malformation in the offspring caused by thalidomide.
 - *Requires Intervention to Prevent Permanent Impairment or Damage* - When the use of a medical product may have resulted in a condition that required medical or surgical intervention to preclude permanent impairment or damage to a patient. Examples: Acetaminophen overdose-induced hepatotoxicity that requires treatment with acetylcysteine to prevent permanent damage; burns from radiation equipment that require drug therapy; breakage of a screw that requires replacement of hardware to prevent malunion of a fractured long bone.
 - *Overdose/Error of Drug or Biologic* - When there is an error or an overdose of a drug or biologic administered as part of a research protocol. Examples: A miscalculation of a drug dose; a mix-up that results in a wrong drug being administered (e.g., placebo instead of intervention drug).

It should be noted that “serious” is not the same as “severe.” The term severe should not be used when reporting events.

4. **Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO):** Any event that is unforeseen, that caused harm or placed a person at increased risk of harm,

and is related to the research procedures. To be defined as an unanticipated problem that involves risks to subjects or others, the event must meet all of the following three criteria:

- **Unanticipated:** The event is unexpected in type, frequency, scope, consequences, or severity; or, if anticipated or referred to in part, is not fully addressed or specified within the initial protocol application, any amendments, consent forms, investigator brochures, minutes, and any existing documentation regarding the research conducted to date under the protocol.
- **Potential for risk** (i.e., caused harm or placed a person at increased risk of harm): As a result of the event, participants or other individuals either are placed or are likely to be placed at physical, psychological, social, or emotional harm that has increased since the time the research was approved by the IRB. An event may qualify as a UP even if no actual harm to subjects or others occurred.
- **Related or possibly related to the research:** The event, situation, or issue arises from the conduct of the research and is of concern for the research participants or others directly affected by the research. Problems may:
 - Be attributable to the conduct of the research, or
 - Result from failures or errors in general systems outside of the research, or factors that are not controlled by the researcher under the protocol, but on which ethical conduct of the research depends, according to the protocol

Unexpected, research-related serious adverse events are included among the unanticipated problems to be reported; however, not all unanticipated problems are adverse events.

Not all unanticipated problems are the result of the investigator's conduct of the research. They may result from changes in a subject's status, such as when a subject becomes pregnant (or fathers a child) contrary to the instructions given by the PI and in the consent/parental permission form or assent; or when a child is transferred from their parents/guardians to foster care (child becomes a ward of the state). Unanticipated problems may also arise from general system failures (e.g., external laboratory errors) over which the investigator has no control.

5. **Unexpected Adverse Event (UAE):** An event in which any of the following apply:
- The specificity or severity is not consistent with the current Investigator Brochure.
 - The event is not consistent with the risk information described in the general investigational plan or elsewhere in the current protocol application.
 - The event is occurring more frequently than anticipated.
 - Examples: Hepatic necrosis may be considered an unexpected event (by virtue of severity) if the protocol only referred to elevated hepatic enzymes or hepatitis. Other examples include cerebral thromboembolism and cerebral vasculitis. These events would be unexpected (by virtue of greater specificity) if the protocol only listed cerebral vascular incidents.

II. **PROCEDURE:**

Refer to the attached [Reportable New Information \(RNI\) Decision Charts](#) for a quick guide to identifying the events and information that must be reported to the Children's National IRB and the timeframe for submitting reports.

A. Unanticipated Problems, Including Unexpected Severe Adverse Events

In general, investigators must report to the IRB any event that is:

- **Unexpected** in type, severity, or frequency;
 - **Related or possibly related** to participation in the research; and
 - **Serious**, or otherwise suggests that the research **places subjects or others at greater risk** of physical, psychological, economic, or social harm than previously known or recognized (i.e., indicates new or increased risks to subjects or others)
1. Reportable unanticipated problems (UPs) can be unexpected, serious adverse events as well as non-clinical events which indicate greater risks to a subject. For example, a data breach or unauthorized disclosure of HIPAA information is a UP. In general, risks which are described in the informed consent document, Investigator Brochure, or package insert are anticipated and, therefore, would not be reported unless they are of a different type, are more severe or are more frequent than expected.
 2. UPs can occur within Children’s National or externally. Here are two examples of events that should be reported to the Children’s National IRB:
 - A subject comes from another part of the country to receive experimental gene therapy and transplantation at Children’s National, but follow-up care and research visits occur at their local hospital. An unanticipated serious adverse event leads to the subject’s hospitalization at the local hospital.
 - A processing error at an external lab produces incorrect results that place a Children’s National subject at risk.

(NOTE: When Children’s National is the IRB of record for one or more external sites, UPs occurring at those research sites should also be reported to the Children’s National IRB.)

3. Study sponsors, coordinating centers, and monitoring entities of multisite studies frequently provide investigators with reports of subject deaths and other serious adverse events that involve subjects who are not Children’s National patients. Investigators should review these reports to determine whether they indicate an increased risk for Children’s National subjects. If there is no change in risks or study procedures for Children’s National subjects as a result of these adverse events, do not report them to the Children’s National IRB. If a sponsor requires these events be reported to the Children’s National IRB, study teams should provide this policy and procedure to the sponsor as justification for not doing so.
 - a) If an external adverse event(s) suggests that Children’s National subjects are at greater risk of harm, changes to the protocol or consent documents are warranted, and it is consistent with the monitoring plan described in the protocol, the investigator is responsible for submitting a modification to the IRB (RA:HRPP:05.10 Protocol Modifications.)
4. Only unanticipated problems which pose increased risks and are related to the research should be reported to the IRB. **Adverse events that are not unanticipated problems do not require reporting to the Children’s National IRB.** These include:
 - Known or foreseeable adverse events associated with the procedures involved in the research and described in the IRB-approved research protocol, any applicable investigator brochure/device manual, current IRB-approved informed consent documents, and other relevant sources of information such as product labeling and package inserts;

- Adverse events due to the expected natural progression of subject’s underlying disease, disorder, or condition and the subject’s predisposing risk factor profile for the adverse event.
- Adverse events due to procedures not directed by the study protocol.

B. Protocol Deviations

Any departure from the protocol that occurs without prior IRB approval and is identified retrospectively is called a deviation. These include deviations from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject. Protocol deviations are classified as either *major/significant* or *minor*, based on both the direct or potential effect of the action or process on the specific subject(s) and the entire subject population, and/or on the overall integrity of the study design and results. *See the Policy section of this document for examples of major and minor protocol deviations.*

All deviations are to be reported to the IRB.

C. Other Reportable Events

In addition to the unanticipated problems and protocol deviations described above, other events and information which require reporting to the IRB include:

- Suspension or termination of the research by the sponsor, investigator, institution, or federal agency. (Exception: pre-planned protocol holds do not need to be reported.) The report must include the reason for study suspension/ termination (see RA:HRPP:11.04 Protocol Suspension, Termination, and Administrative Closure policy and procedure).
- Non-compliance or alleged non-compliance with federal regulations, CNH policies/procedures, or IRB requirements or determinations (e.g., multiple lapses in IRB approval). (See RA:HRPP:11.02 Investigator Noncompliance: Investigations and Determinations policy and procedure.)
- Audit, inspection, or inquiry by a federal agency, whether or not any issues are found.
- Written report by Data Safety and Monitoring Board (DSMB), Data Monitoring Committee (DMC), or equivalent monitoring entity if any significant issues are identified. If there are no significant findings and the study will proceed without changes, the monitoring report can be submitted at the time of continuing review.
- Incarceration or other involuntary commitment of a subject participating in a study not approved by the IRB to include prisoners.
- Subject or family member complaint that cannot be resolved by the study team, including any complaints referred to the Research Subject Advocate (RSA).

D. Timeframes for reporting events and information to the Children’s National IRB

1. **The investigator must report to the Children’s National IRB within one (1) business day of learning of the event:**

- a) The unexpected death of a Children’s National subject that is related or possibly related to their participation in a research study. Follow-up reports should be submitted within one (1) business day of new information becoming available. Additional follow-up reports may also be required at the discretion of the IRB Chair or convened IRB.
 - i. **DO NOT REPORT** the death of a subject at another site unless Children’s National is the IRB of record for the external site. (See [*sIRB guidance document link*] when Children’s National is the IRB of record for an

external site.)

- b) Any data breach or HIPAA violation. This includes the loss, theft, hacking, or other unauthorized disclosure of private health information (PHI) or confidential data. Some examples include the theft of a laptop containing data files with subjects' PHI, inadvertent disclosure of subject identifiers in an email, or unauthorized inclusion of identifiers with samples sent to a research collaborator at another site. Additional follow-up reports may also be required.
2. **The investigator must report to the Children's National IRB within seven (7) business days of learning of the event:**
 - a) Nonterminal unanticipated serious adverse events. *See the Policy section of this document for a definition of Serious Adverse Event (SAE).* Additional follow-up reports may also be required at the discretion of the IRB Chair or convened IRB. Note: Investigators' obligation to report serious adverse events that are unexpected and related or possibly related to the research continues even after the study has been closed.
 - b) *Major* protocol deviations
 - c) Other reportable events and information
 3. **The investigator must report *minor* protocol deviations to the Children's National IRB at the time of continuing review.** If a study does not require continuing review by the IRB, minor protocol deviations should be reported at least yearly before the study team submits the Annual Progress Update.

Additional follow-up reports may also be required at the discretion of the IRB Chair or convened IRB.

E. Investigator Responsibilities

Refer to the attached [Reportable New Information \(RNI\) Decision Charts](#) for a quick guide to identifying the events and information that must be reported to the Children's National IRB and the timeframe for submitting reports.

1. Investigators must report unanticipated problems, major protocol deviations, and other qualifying events and information by creating and submitting Reportable New Information (RNI) in IRBear 2.0. A detailed description of the event should be attached and include:
 - Date the event occurred;
 - Date the investigator learned of the event;
 - Number of Children's National subjects affected;
 - When warranted, a detailed corrective and preventive actions (CAPA) plan describing how the current event will be addressed and what steps will be taken to prevent similar events from occurring in the future

Investigators should attach any relevant documentation to the RNI submission, being sure to redact any information that could identify the subject(s) involved.

2. Investigators must adhere to the timelines for reporting information/events to the IRB.
3. Investigators are responsible for carrying out all actions required by the IRB including, when applicable, notifying study subjects about the protocol deviation, other follow-up

actions in response to the event being reported, and actions to prevent similar future protocol deviations.

4. In addition to reporting these events to the Children’s National IRB, investigators must also comply with FDA, study sponsor/funding agency, and external IRB reporting requirements, as applicable.

F. OPHS and IRB Responsibilities

1. An IRB Regulatory Analyst will conduct an administrative pre-review of an RNI submission to ensure it is complete. Reports which are incomplete or require clarifications will be returned to the investigator for corrections or additional information. Once the investigator has satisfactorily responded to any requests for changes and the Analyst has completed the pre-review process:
 - a) RNIs which report unanticipated problems will be scheduled for a convened meeting.
 - b) RNIs which report what appears to be serious and/or continuing noncompliance will be investigated as described in RA:HRPP:11.02 *Investigator Noncompliance: Investigations and Determinations* policy and procedure. If warranted, the event or information will be reported to the convened IRB.
 - c) The remaining RNIs will be assigned to a designated IRB member for expedited review. The designated reviewer will refer to the convened IRB any RNI they believe may represent a UP or serious and/or continuing investigator noncompliance, or otherwise raises concerns about the conduct of the research.
2. At a convened meeting, the IRB will determine whether an RNI meets the criteria for an unanticipated problem involving risks to subjects or others and/or investigator noncompliance with the IRB-approved protocol, institutional policies and procedures, or regulations governing human subject protections. These determinations can be made only by the full board.
 - a) If a determination of noncompliance is made, the convened IRB will decide whether the reported event(s) constitute serious or continuing noncompliance (RA:HRPP:11.02, *Investigator Noncompliance: Investigations and Determinations*).
3. For both a convened meeting and designated review, determinations will be made, as applicable, regarding whether:
 - a) Information should be provided to subjects (generally when such information might relate to their willingness to continue to take part in the research);
 - b) Reconsent is required and, if so, whether past and/or current subjects should be reconsented;
 - c) Any corrective and preventive actions (CAPA) plan proposed by the investigator to address the current issue and prevent future occurrences are appropriate and sufficient; or, if none is provided, whether a CAPA plan is required
4. Once the convened IRB or designated reviewer completes their review of the RNI and, if applicable, accepts that appropriate follow-up actions have occurred, an official acknowledgement will be sent to the Principal Investigator, their proxy(ies), and the primary contact for the study.

5. Depending upon the findings of the IRB, it may be necessary to report an event to external agencies as outlined in RA:HRPP:11.05 *Mandatory Reporting to External Agencies* policy and procedure.

III. **ACCOUNTABLE EXECUTIVE(S) AND REVIEWER(S)**

- a. Accountable Executive: Chief Academic Officer/Institutional Official for the Federalwide Assurance
- b. Department Responsible for Review: Office for the Protection of Human Subjects
- c. Committee Responsible for Review: Institutional Review Board Executive Committee

IV. **APPROVAL**

Approved by:

_____ IRB Executive Committee	_____ 10/29/2009 Date
_____ Vittorio Gallo, PhD, Chief Academic Officer	_____ Date

V. **APPLICABILITY**

Children's Research Institute, Children's National Medical Center

Persons to whom the policy and procedure applies: Investigators, Institutional Review Board, Office for the Protection of Human Subjects

VI. **REVIEW OR REVISION DATE**

Original: 10/29/2009
Revised: 11/7/2014
Revised: 3/14/2018
Revised: 10/11/2022

VII. **REFERENCES**

Policies and Procedures:

- Replaces previous policies and procedures RA:HRPP:06.02, *Unanticipated Problems Including Serious Adverse Events* and RA:HRPP:05.07, *Protocol Deviations*
- RA:HRPP:05.10 *Protocol Modifications*
- RA:HRPP:11.02 *Investigator Noncompliance: Investigations and Determinations*
- RA:HRPP:11.05 *Mandatory Reporting to External Agencies*

Forms and Guidance:

- [Reportable New Information \(RNI\) Decision Charts](#)
- [Unanticipated Problems Involving Risks & Adverse Events Guidance \(2007\) | HHS.gov](#). Accessed 10/11/2022.

Federal Regulations:

- Department of Health and Human Services (DHHS) 45 CFR 46.108(a)
- U.S. Food and Drug Administration (FDA) 21 CFR 56.108(a)(4)

Reportable New Information (RNI) Decision Charts

These charts are designed as a guide for study teams to identify events that must be reported to the IRB as Reportable New Information (RNI) and the timeframe for reporting them. They are nonbinding generalizations and may not be specific enough for all situations. Contact OPHS@childrensnational.org if you have questions.

In addition to the adverse events, unanticipated problems, and protocol deviations specified in these decision trees, study teams are required to submit an RNI within 7 business days to report the following events to the IRB:

- **Suspension or termination** of the research by the sponsor, investigator, institution, or federal agency (Exception: pre-planned protocol holds do not need to be submitted as an RNI);
- **Non-compliance or alleged non-compliance** with federal regulations, CNH policies/procedures, or IRB requirements or determinations (e.g., expiration of IRB approval);
- **Audit**, inspection, or inquiry by a federal agency, whether or not any issues are found;
- **Written report** by Data Safety and Monitoring Board (DSMB), Data Monitoring Committee (DMC), or equivalent monitoring entity if any significant issues are identified (if there are no significant findings and the study will proceed without changes, the report can be submitted at the time of continuing review);
- **Incarceration** or other involuntary commitment of a subject participating in a study not approved by the IRB to include prisoners;
- **Subject or family member complaint** that cannot be resolved by the study team, including any complaints referred to the Research Subject Advocate (RSA)

The IRB may additionally require corrective and preventive action (CAPA) plans and/or follow-up reports.

Study teams must also comply with FDA, study sponsor/funding agency, and external IRB reporting requirements, as applicable.

Reportable New Information (RNI) Decision Charts

CHART 1: Adverse Events

Study teams must comply with FDA, study sponsor/funding agency, and external IRB reporting requirements, as applicable, in addition to submitting RNIs to the CNH IRB.

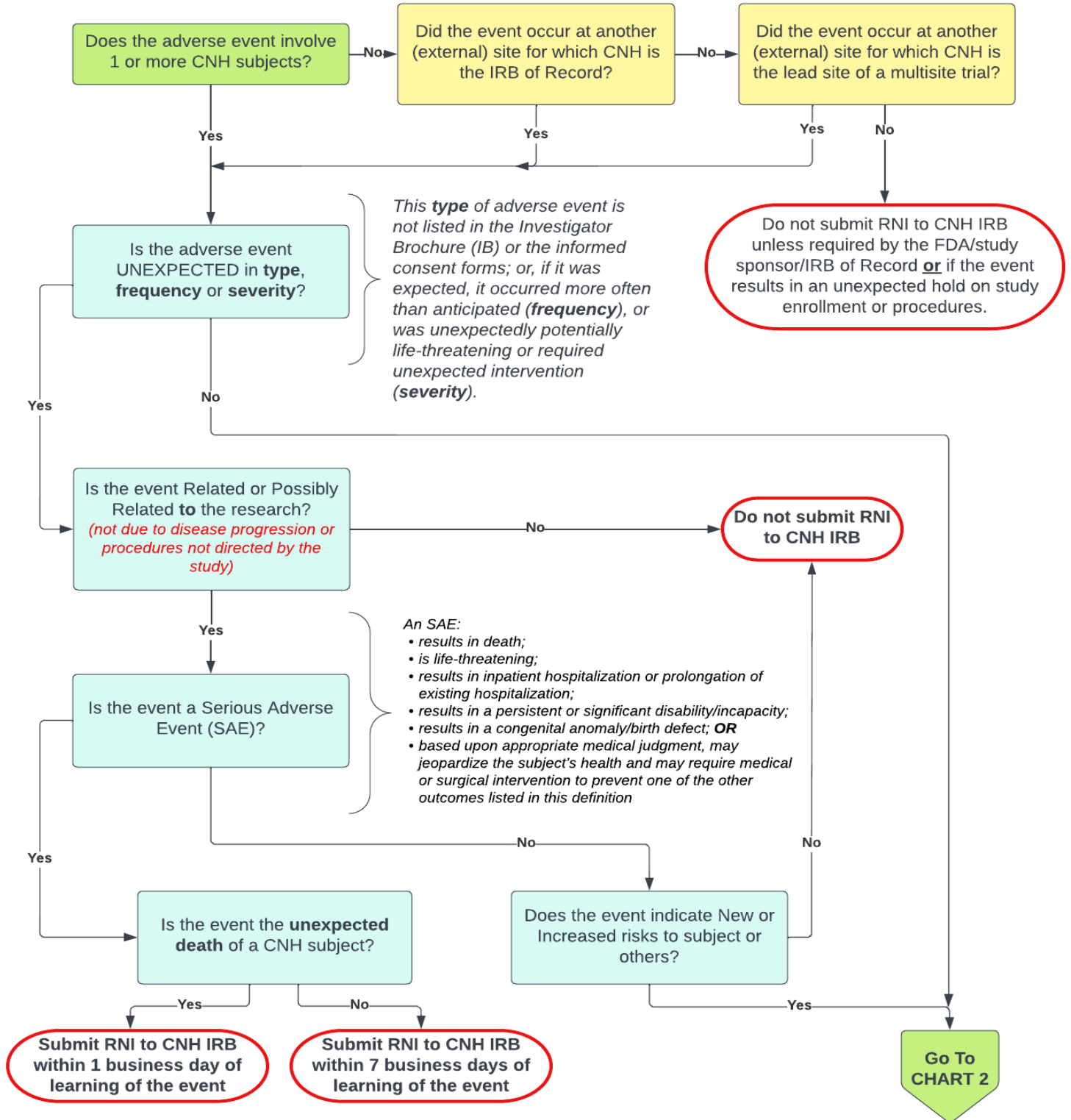


CHART 2: Non-AE Unanticipated Problems and Protocol Deviations

Study teams must comply with FDA, study sponsor/funding agency, and external IRB reporting requirements, as applicable, in addition to submitting RNIs to the CNH IRB.

