NCI COOPERATIVE GROUP TRIALS

Maria Davenport, MPH, CCRC
Clinical Research Educator
Office of Clinical Research

ACCREDITATION

- The University of Virginia School of Medicine and School of Nursing awards **1.0 contact hour** for nurses who participate in this educational activity and complete the post activity evaluation.
- The University of Virginia School of Medicine and School of Nursing awards **1.0 hour of participation** (consistent with the designated number of AMA PRA Category 1 Credit(s)™ or ANCC contact hours) to a participant who successfully completes this educational activity. The University of Virginia School of Medicine and School of Nursing maintains a record of participation for six (6) years.

DISCLOSURES

Full Disclosure Policy Affecting CME Activities: As a joint accredited provider, the University of Virginia Office of CME/CE requires attested and signed global disclosure of the existence of all financial interests or relationships with commercial interest from any individual in a position to control the content of a CME activity sponsored by OCME.

Disclosure Summary:

No one in a position to control the content of this educational activity has disclosed a relevant financial interest or relationship with any commercial interest

DISCLAIMERS

Some of the content included is based on the experience/background of the presenter, and is somewhat subjective.

Presentation was prepared prior to NIH freeze. As of the time of the current presentation, 28JAN2025, it is unclear how the freeze will impact NCI trials.

https://www.science.org/content/article/trump-hits-nih-devastating-freezes-meetings-travel-communications-and-hiring

ACTIVITY CODE

Activity Code: 27051

Instructions for claiming credits/contact hours can be found here.

OUTLINE

- Evolution/Background of NCI Cooperative Groups
- Operations
- Adverse Events
- Data Quirks
- Audits

EVOLUTION OF NCI COOPERATIVE GROUPS

NCI COOPERATIVE GROUP TRIALS

A cooperative group in oncology is a network of researchers and doctors from different organizations, cancer centers, and communities who work together to create and conduct clinical trials for cancer prevention, treatment and care delivery.

KEY COOPERATIVE GROUPS

SWOG

Southwestern Oncology Group

Focuses on adult cancers and conducts clinical trials to improve cancer treatment and prevention

ALLIANCE

Focuses on adult cancers and conducts clinical trials to improve cancer care through innovative research

ECOG-ACRIN

Eastern Cooperative Oncology Group:

Focuses on adult cancers and conducts multi-disciplinary clinical trials to develop develop new cancer treatments and diagnostic tools

ETCTN

Experimental Therapeutics Clinical Trials Network

Conduct early clinical trials of NCI-IND agents in high priority areas of unmet medical needs

COG

Children's Oncology Group

Focuses on childhood cancers and conducts clinical trials to develop new treatments and improve outcomes for pediatric cancer patients

NRG ONCOLOGY

Consortium of three groups (NSABP, RTOG, GOG)

Focuses on adult cancers and conducts clinical trials to improve radiation therapy, surgical techniques and other cancer treatments.

INTRODUCTION TO NCI COOPERATIVE GROUP TRIALS

PURPOSE OF NCI COOPERATIVE GROUP TRIALS

Large-scale, multi-institutional clinical studies designed to evaluate new cancer treatments and improve the standard of care for cancer patients.

HISTORY OF NCI COOPERATIVE GROUP TRIALS

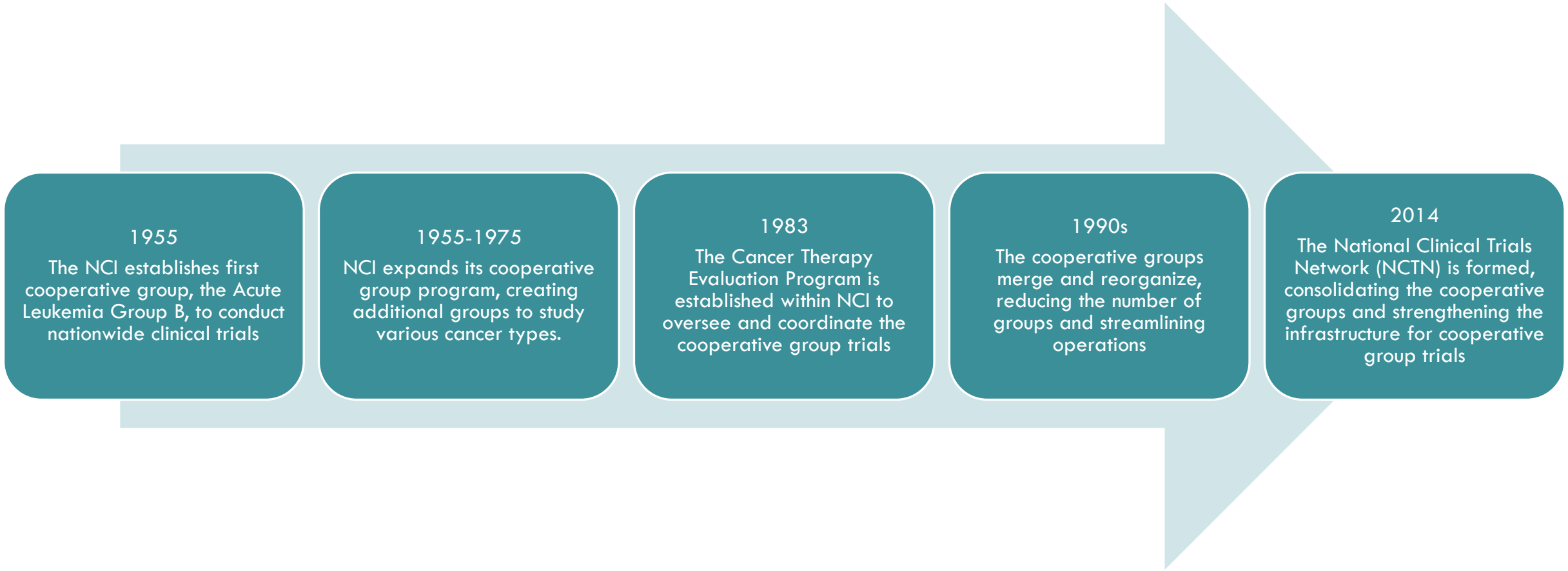
Established in the 1950s to facilitate cancer research collaboration and accelerate the development of new cancer therapies. One of the the goals was to explore rare cancers.

STRUCTURE OF NCI COOPERATIVE GROUP TRIALS

Organized and conducted by collaborative networks of cancer research institutions, including academic centers, community hospitals, and the NCI.

IN SUMMARY, NCI COOPERATIVE GROUP TRIALS PLAY A CRUCIAL ROLE IN ADVANCING CANCER RESEARCH AND IMPROVING PATIENT OUTCOMES BY FACILITATING LARGE-SCALE, COLLABORATIVE CLINICAL STUDIES THAT EVALUATE NEW CANCER TREATMENTS AND REFINE THE STANDARD OF CARE.

THE EVOLUTION OF NCI COOPERATIVE GROUP TRIALS



PROS OF NCI COOPERATIVE GROUP TRIALS

- Diverse patient population [1]
- Robust infrastructure [1]
- Multi-institutional collaboration [1]
- Accelerated drug development [1, 2]
- Address secondary endpoints such as QoL [1]
- Public Health impact: Cooperative Group trials have contributed substantial gains in life-years for cancer patients and have had a significant scientific impact [3]
- *Fewer "bells & whistles" compared to industry-sponsored studies

* = no citation/ speaker's opinion

CONS OF NCI COOPERATIVE GROUP TRIALS

- Lengthy study-wide approval process[1]
- Funding constraints [1]
- Regulatory burden: Expanding regulatory requirements and increasing operational complexity have created significant headwinds for the Cooperative Groups [1]
- Bureaucratic inefficiencies and expansive bureaucracy [2]
- Restrictive eligibility criteria: been a major hurdle for many patients wanting to participate in NCI trials [3]
- *Lack of flexibility, accountability (from CRAs) and study support compared to industry-sponsored studies
- * Data/ data management can be more confusing

OPERATIONS

HELPFUL TERMS – CLINICAL TRIAL MANAGEMENT & SUPPORT SYSTEMS

Cancer Therapy Evaluation Program
Oversees the design, conduct, and analysis of cancer clinical trials.

CTEP

Cancer Trials Support Unit
Supports NCI clinical trials, providing access to trial information, enrollment, and trial management resources. Website to access trial content.

CTSU

Clinical Trial Management System
Software used to plan, track, and manage the logistics and data of clinical trials.

CTMS

Registration & Credential Repository
A database that stores information on the registration and credentials of individuals involved in clinical trials.

RCR

Adverse Event Reporting System
Tool used to report, track, and manage adverse events in clinical trials, ensuring proper documentation and regulatory compliance. Website where SAEs are entered.

CTEP AERs

Identity and Access Management
Part of the Cancer Therapy Evaluation Program, this system manages user identities and access control for various clinical trial platforms.

CTEP – IAM

Oncology Patient Enrollment Network
A network that facilitates the enrollment of patients into oncology clinical trials, streamlining the process for both patients and providers.

OPEN

National Clinical Trials Network
Helps these organizations develop new clinical trials and manage their regulatory, financial, membership, and scientific committees.

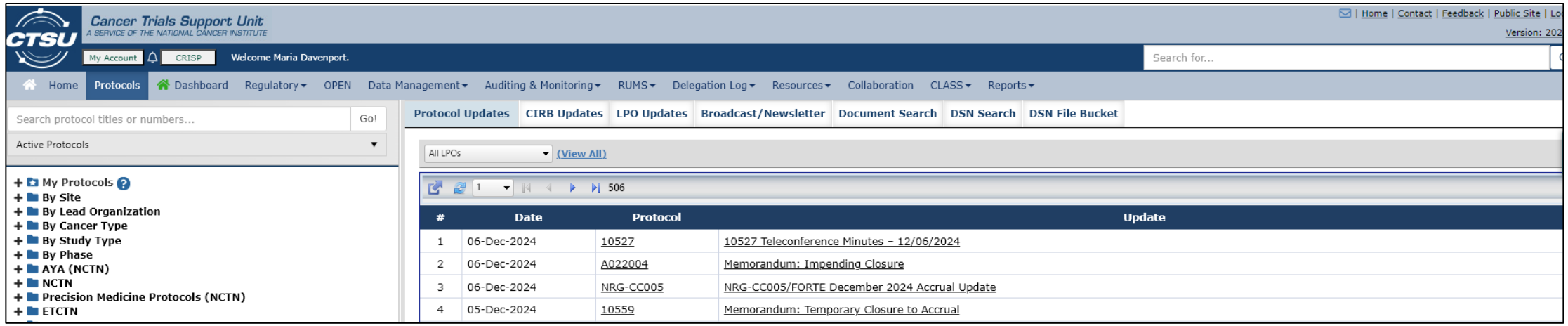
NCTN

STUDY START-UP

- Study-start up for cooperative group trials is faster than pharmaceutical studies.
  - Reasons for expedited process at UVA:
    - We bypass the full PRC approval process for NCI studies (and is solely reviewed by the PRC chair). Therefore, it takes an average of 1 month to open an NCI study, at least from a regulatory perspective.
    - The study has already been approved by NCI CIRB when we submit for approval, so they only have to approve our site.
    - UVA has overall agreements in place with cooperative group studies so there is no study-specific contract to negotiate.
    - Cooperative group studies provide non-negotiable budgets.
- They typically don't have a formal SIV, and if they do, it is usually just a one-hour meeting to review highlights. ETCTN tends to have more SIVs (also called site initiation training/SIT) than other groups.

CTSU

- General portal for all content related to cooperative group trials is found at CTSU.org.
- Must make sure your RCR profile (Registration & Credential Repository with NCI) isn't expired, otherwise you won't be able to register patients.
  - If you go to "My account" on the CTSU homepage, it'll tell you when your registration expires. They also send out emails when your account is close to expiration. Don't wait till the last moment!
  - If you have issues with this process, reach out to your reg coordinator or Kirsten Bugden for help.



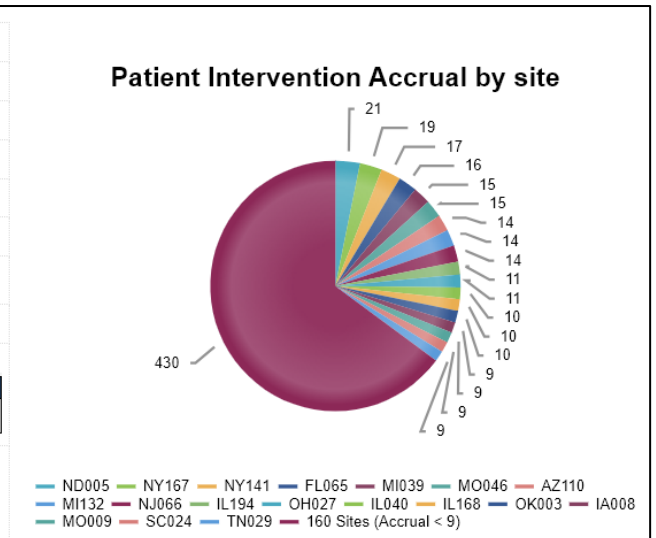
CTSU

- Status updates & enrollment summaries
- Protocol/consent forms **(they don't include the UVA-approved language, so still refer to Florence for official documents)**
- Sample collection guidelines
- Protocol forms, such as eCRF guidelines
- Funding information

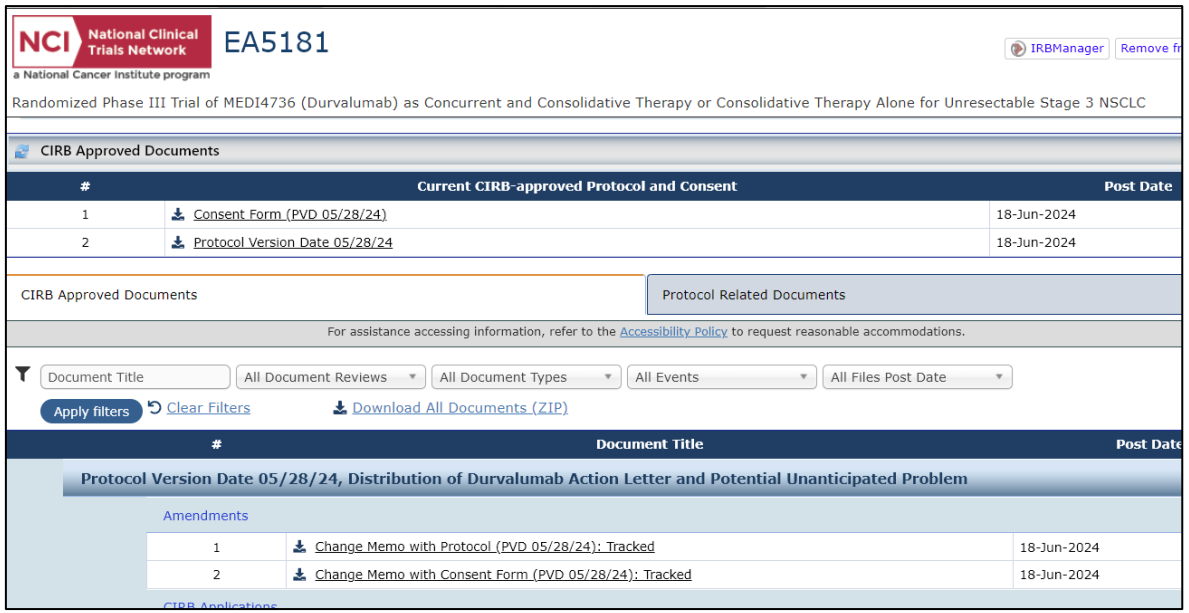
Protocol Status:	CLOSED TO ACCRUAL
Protocol Status Date:	20-Nov-2023
Activation Date:	09-Apr-2020
Lead Organization:	ECOG-ACRIN
NCI Program:	NCTN
Phase:	III
Country Participation:	
ClinicalTrials.gov Link:	NCT04092283
Patient Accrual:	As of 10-Dec-2024 10:15:17 AM

Step Type	Step(s)	Planned	Actual
Intervention	1	660	663

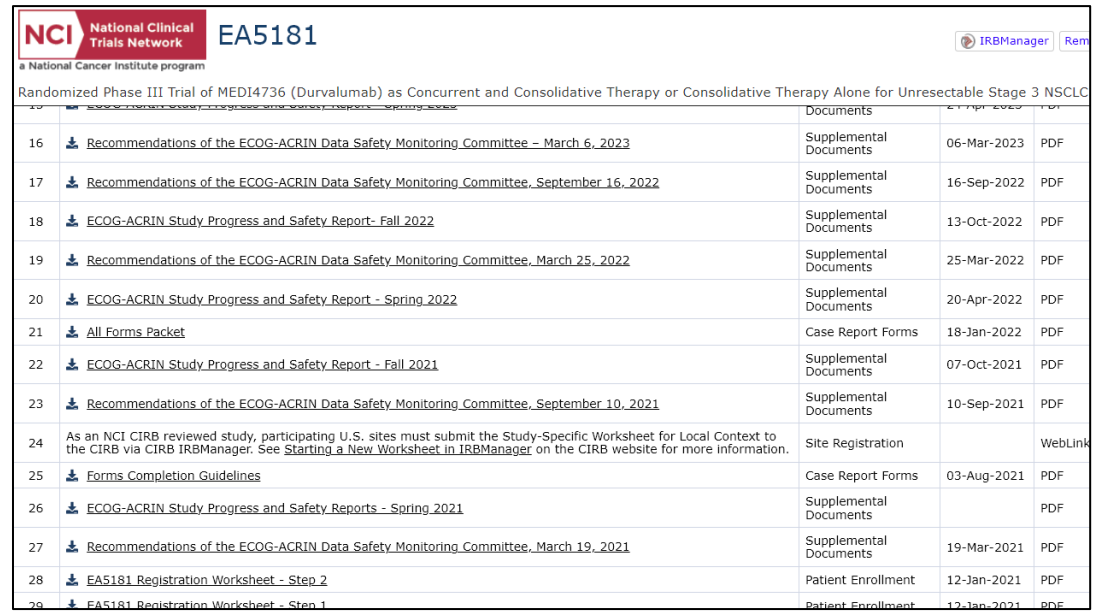
Study Champions: Masters, Andrew Gregory NRG; Ross, J Helen ALLIANCE; Harkenrider, M. Matthew SWOG



CTSU



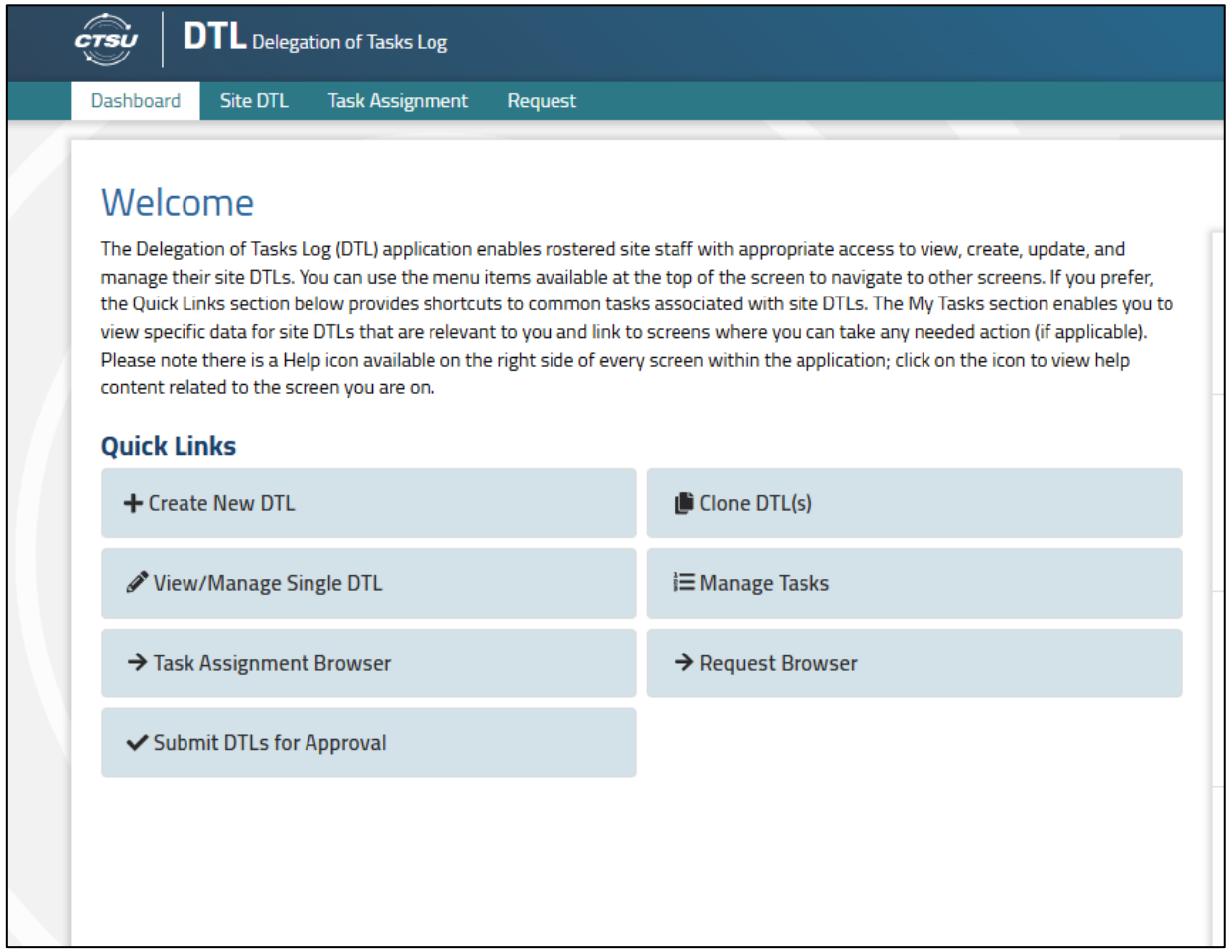
Access protocol/consents, memos etc.



Access to study materials, such as eCRF guidelines (referred to as “all forms packet”), registration info etc.

CTSU

- CTSU houses many of the NCI DOA logs. They're referred to as "DTL" (delegation of tasks log).
- For studies that don't require DTLs, the OCR practice is to maintain a DOA in Florence. Older studies had a separate process using DocuSign.
- The institutional PI must sign off on each staff members delegated tasks prior to them being able to complete tasks such as registration.
- Reg team manages the DTLs for OCR.



PROTOCOL REQUIREMENTS

Protocol Specific Requirements (PSR)

#	Description	Submission Type	Source	Required for Enrollment?	Required by Date	LPO Review required?	Applicable Cou
1	IRB Approval	Specific Site(s) and Protocol(s)	CIRB	✓	Prior to Enrollment		ALL
2	ETCTN Specimen Tracking Training	Specific Person(s) Only	SITE	✓	Prior to Enrollment		ALL
3	Site Initiation Visit	Specific Site(s) and Protocol(s)	LPO	✓	Prior to Enrollment		ALL

Protocol Specific Requirements (PSR)

#	Description	Submission Type	Source	Required for Enrollment?	Required by Date	LPO Review required?	Applicable Countrie
1	IRB Approval	Specific Site(s) and Protocol(s)	CIRB	✓	Prior to Enrollment		ALL
2	Site Initiation Teleconference (SIT)	Specific Site(s) and Protocol(s)	LPO	✓	Prior to Enrollment		ALL
3	Site DTL	Site DTL Browser tab	DTL	✓	Prior to Enrollment		ALL

- See the protocol requirements section in CTSU to see specific requirements for each study. Here are two examples.

OPEN

- OPEN system is used to register patients for NCI studies.
- They'll often ask you to answer all the eligibility questions to verify eligibility. Note- sometimes the way the eligibility questions are worded differently compared to the protocol, and they might ask separate questions that are unexpected.
- Make sure you save the enrollment confirmation to the subjects records.
- **CTEP ID/Site Number for UVA: VA009**
- You can do a practice enrollment!

Figure 5: Site and Role

a registration for a site or role different from what is displayed, a drop down list will be shown (Figure 6). Use the drop down list t

Figure 6: Site and Role

ome page or click on the Enroll tab and press the 'Create New' option. This will allow you to complete the preliminary steps of the

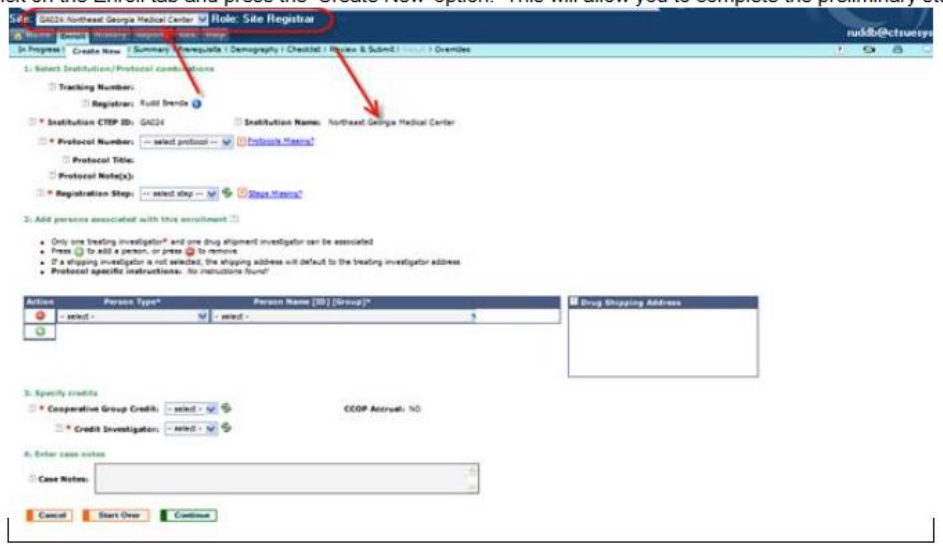
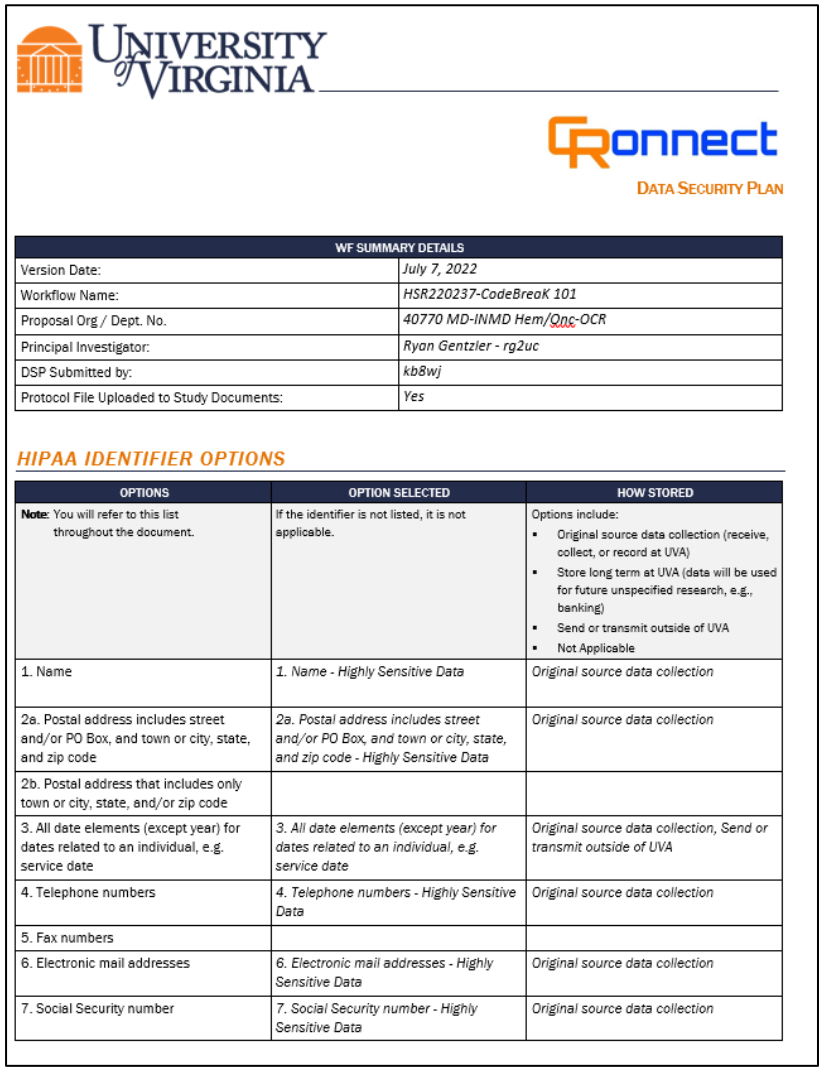


Figure 7: Create New Tab

DATA SAFETY PLAN

- During the registration process, several studies will require a SSN or MRN, you can just include "000000" instead.
- Some studies also require the patients zip code.
- Always double check the DSP before giving out PHI.



UNIVERSITY of VIRGINIA

CRonnect

DATA SECURITY PLAN

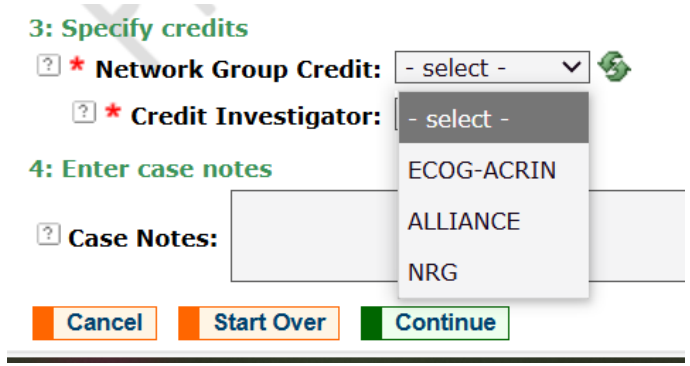
WF SUMMARY DETAILS	
Version Date:	*July 7, 2022*
Workflow Name:	*HSR220237-CodeBreaK 101*
Proposal Org / Dept. No.	*40770 MD-INMD Hem/Onc-OCR*
Principal Investigator:	*Ryan Gentzler - rg2uc*
DSP Submitted by:	*kb8wj*
Protocol File Uploaded to Study Documents:	*Yes*

HIPAA IDENTIFIER OPTIONS

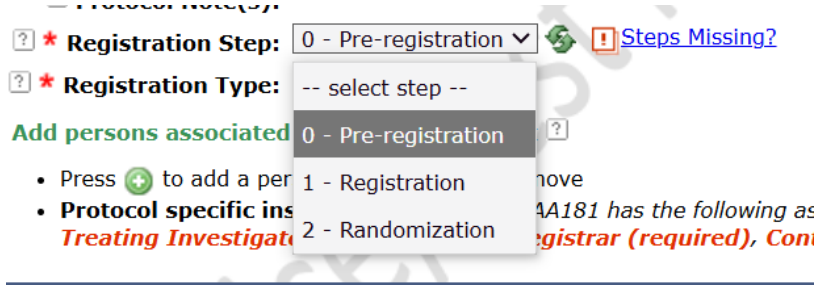
OPTIONS	OPTION SELECTED	HOW STORED
Note: You will refer to this list throughout the document.	If the identifier is not listed, it is not applicable.	Options include: ▪ Original source data collection (receive, collect, or record at UVA) ▪ Store long term at UVA (data will be used for future unspecified research, e.g., banking) ▪ Send or transmit outside of UVA ▪ Not Applicable
1. Name	*1. Name - Highly Sensitive Data*	*Original source data collection*
2a. Postal address includes street and/or PO Box, and town or city, state, and zip code	*2a. Postal address includes street and/or PO Box, and town or city, state, and zip code - Highly Sensitive Data*	*Original source data collection*
2b. Postal address that includes only town or city, state, and/or zip code		
3. All date elements (except year) for dates related to an individual, e.g. service date	*3. All date elements (except year) for dates related to an individual, e.g. service date*	*Original source data collection, Send or transmit outside of UVA*
4. Telephone numbers	*4. Telephone numbers - Highly Sensitive Data*	*Original source data collection*
5. Fax numbers		
6. Electronic mail addresses	*6. Electronic mail addresses - Highly Sensitive Data*	*Original source data collection*
7. Social Security number	*7. Social Security number - Highly Sensitive Data*	*Original source data collection*

PATIENT REGISTRATION

- When you register a patient, it'll often ask which "registering group" you want to give credit to.
  - If there is more than 1 option, typically you should give credit to whichever group the study is run by. For example, if it's ECOG, then you give credit to ECOG. However, this varies, so please ask your AD for guidance for each trial.



- You may also be required to choose a registration step (i.e. Step 0, 1, 2).
  - " Step 0" - Pre-registration is often an administrative step used for studies that require a study ID prior to enrollment to allow for submission of central blood or tissue samples.
  - FYI! If step 0 is not an option be mindful that completing step 1 prior to confirming eligibility could potentially enroll an ineligible patient.

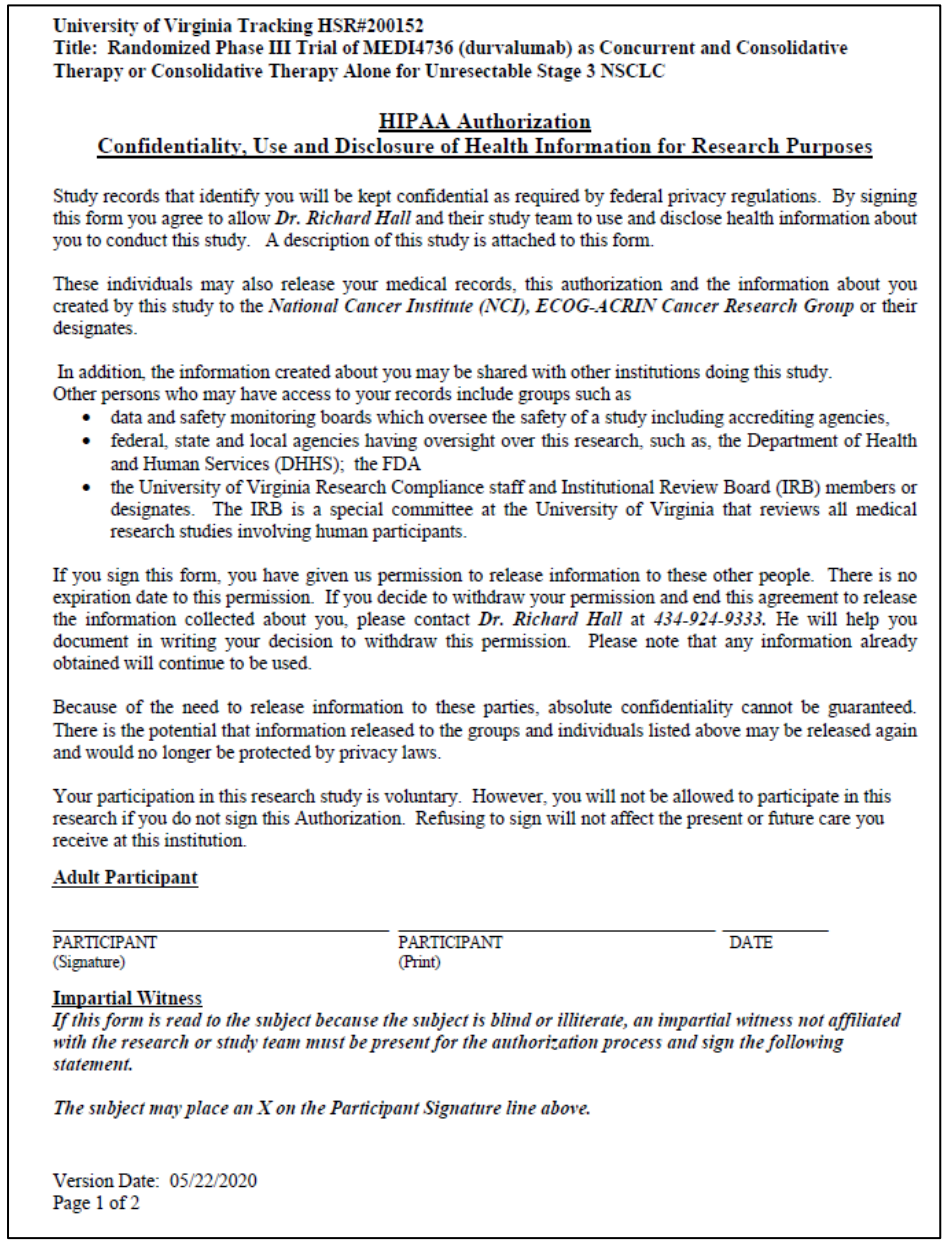


PATIENT ENROLLMENT

- NCI studies never offer exemptions, exceptions, waivers for enrollment or any other protocol-required procedures/tasks etc.
  - For example: I (Maria) had a patient with grade 3 lymphocyte count decrease that the doctor didn't care about, and ECOG said they couldn't enroll since all of their previous treatment-related AEs hadn't resolved to a G2 or better. Many industry sponsors would be fine with this since the patient still met the lab parameters explicitly described in the eligibility parameters.

CONSENT

- Cooperative group studies require the use of a free-standing HIPAA consent authorization.
- The patient should sign it at the same time as their initial consent.
- Rationale: cooperative group studies are conducted at many different institutions and it would be challenging for the IRB of record to incorporate each site's own privacy language. Also, NCI NCIRB doesn't have a HIPAA Privacy Board.



University of Virginia Tracking HSR#200152
Title: Randomized Phase III Trial of MEDI4736 (durvalumab) as Concurrent and Consolidative Therapy or Consolidative Therapy Alone for Unresectable Stage 3 NSCLC

HIPAA Authorization
Confidentiality, Use and Disclosure of Health Information for Research Purposes

Study records that identify you will be kept confidential as required by federal privacy regulations. By signing this form you agree to allow ***Dr. Richard Hall*** and their study team to use and disclose health information about you to conduct this study. A description of this study is attached to this form.

These individuals may also release your medical records, this authorization and the information about you created by this study to the *National Cancer Institute (NCI), ECOG-ACRIN Cancer Research Group* or their designates.

In addition, the information created about you may be shared with other institutions doing this study.
Other persons who may have access to your records include groups such as

- data and safety monitoring boards which oversee the safety of a study including accrediting agencies,
- federal, state and local agencies having oversight over this research, such as, the Department of Health and Human Services (DHHS); the FDA
- the University of Virginia Research Compliance staff and Institutional Review Board (IRB) members or designates. The IRB is a special committee at the University of Virginia that reviews all medical research studies involving human participants.

If you sign this form, you have given us permission to release information to these other people. There is no expiration date to this permission. If you decide to withdraw your permission and end this agreement to release the information collected about you, please contact ***Dr. Richard Hall*** at *434-924-9333.* He will help you document in writing your decision to withdraw this permission. Please note that any information already obtained will continue to be used.

Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. There is the potential that information released to the groups and individuals listed above may be released again and would no longer be protected by privacy laws.

Your participation in this research study is voluntary. However, you will not be allowed to participate in this research if you do not sign this Authorization. Refusing to sign will not affect the present or future care you receive at this institution.

Adult Participant

_____	_____	_____
PARTICIPANT (Signature)	PARTICIPANT (Print)	DATE

Impartial Witness
If this form is read to the subject because the subject is blind or illiterate, an impartial witness not affiliated with the research or study team must be present for the authorization process and sign the following statement.

The subject may place an X on the Participant Signature line above.

Version Date: 05/22/2020
Page 1 of 2

BUDGET/FUNDING

- Generally the budget is non-negotiable, and they dictate which procedures are standard of care. Typically we get $3k per patient for NCI studies, with ETCTN offering approximately $7-$8k.
  - In contrast, some of our more generous sponsors might pay around $3k per patient visit, and also allow invoicing for other procedures such as scans/biopsies.
- In general, we are paid for work completed/enrollments. The more we enroll, the more money we are paid. NCI doesn't offer any administrative fees like industry studies.
- UVA receives approx. $25M/year in funds from NCI to help support research. A lot of this funding also supports bench science research.

BUDGET/FUNDING

- Some cooperative group studies will have funding that is only available if the patient participates in specific procedures (such as surveys/optional biopsies). This may require CRC to fill in the OPEN funding tab. ETCTN has not used this feature.
- We have 1 year from the date of completion to update the billing in order to get paid.
- OCR CRCs- must add a prompt on CRC checklist to complete OPEN funding.

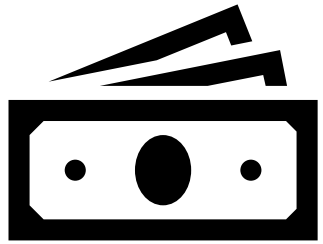
Funding Source and Study Component		Collect Type	Study Specific Notes	Enter Date in Open? (c)	NCTN Funding per Patient (a) Std/HP LAPS	NCORP Funding per Patient (b) Std/HP
Federal	Base Intervention – Standard / High Performance LAPS & NCORP	Mandatory		No	$3,600/$5,200	$3,600/$5,200
Federal	Biospecimen – Tissue Archived Tumor Tissue Biopsy Prior to Start of Treatment	Optional	1	Yes	$100	$100
Federal	Biospecimen – Peripheral Blood Up to 7 timepoints: before treatment, Step 1 CRT (Wks 3 & 5), Step 2 Consolidation (Cycle 1 Day 1, 3 months, 12 months), recurrence	Optional	1	Yes	$300	$300
Federal	Biospecimen – Tissue Tumor Tissue from Biopsy at Recurrence (performed as Standard of Care)	Optional	1	Yes	$100	$100
Total Potential Federal Funds					**$4,100/$5,700**	**$4,100/$5,700**
Non-Federal	ECG at screening	Conditional	2	Yes	$25	$25
Total Potential Funds					**$4,125/$5,725**	**$4,125/$5,725**

Instructions for completing funding:
https://www.ctsu.org/open/Site_Resources/Training/Users_Manual/FundingScreenSiteUserGuide.pdf

BUDGET/FUNDING

- Why should the budget/funding topic matter for **CRCs**?
  - Clinical research at UVA is "cost-recovery". I.e. staff pay for themselves by enrolling patients.
  - Study budgets support the CRC positions. If we don't have sufficient funding, which requires enrollments, then we can't support as many CRC positions.
  - Be mindful of the amount of effort you spend for cooperative group studies. Talk to manager/Ed coordinator if you think you're spending too much time. We may be able to optimize processes.
  - Strive for efficiency as much as possible to help reduce the amount of effort that is associated with these lower budget studies.
    - Example: pay attention to protocol AE reporting guidelines to determine if abnormal labs need to be reported. This saves a considerable amount of billable time if those don't need to be reported as AEs.

BUDGET/FUNDING



Why the **patient** may be impacted?

- The studies assume which procedures are standard of care vs. research. This can make a considerable difference for patients who are limited with funds, especially since the budgets are non-negotiable.
- These studies generally don't have as many options for hotels/travel etc., so may be harder to enroll patients who aren't local.
- You can speak with Mark Dewey, OCR Clinical Trial Navigator, about potential funding/resources that may be available for these patients. DO NOT promise patients any extra resources outside of what the consent indicates.

CONTACTS & TERMINOLOGY CONFUSION

- Study Chair = PI who is responsible for overseeing the conduct of a clinical trial protocol.
  - Equivalent to study PI or Medical Monitor
  - Their credentials are typically MD/DO or international equivalent
- Protocol Contact or Study Coordinator: An individual who supports the research team by managing the administrative and operational aspects of the clinical trial at a research site.
  - Equivalent to CRA (Clinical Research Associate for pharma studies)
  - Typically their credentials are BS, MPH (or similar degree), CCRC/CCRP, RN. But, they're not generally an advanced practice medical provider
- The EDC may refer to the Clinical Research Coordinator as the "CRA", which indicates "clinical site staff". This contradicts most of our other studies!!
- There are other contacts listed in protocols for data management, specimen submission etc. Review each protocol for details.

CONTACTS

- A common frustration with CRCs is the lack of study contacts and resources.
- A list of contacts is typically found within the first pages of your protocol, similar to the example below.

STUDY CHAIR

Nathan Pennell, M.D, Ph.D
Cleveland Clinic Foundation
Dept. of Hematology and Medical Oncology
9500 Euclid Ave CA6
Cleveland, OH 44195
Phone: (216) 445-9282
Fax: (216) 444-9464
E-Mail: penneln@ccf.org

STUDY CO-CHAIR

John Varlotto, M.D.
Marshall University
Cabell Huntington Medical Center
Edwards Comprehensive Cancer Center – Radiation Oncology
1400 Hall Greer Boulevard
Huntington, WV 25701
E-mail: varlotto@marshall.edu

STUDY CHAIR LIAISON (SCL)

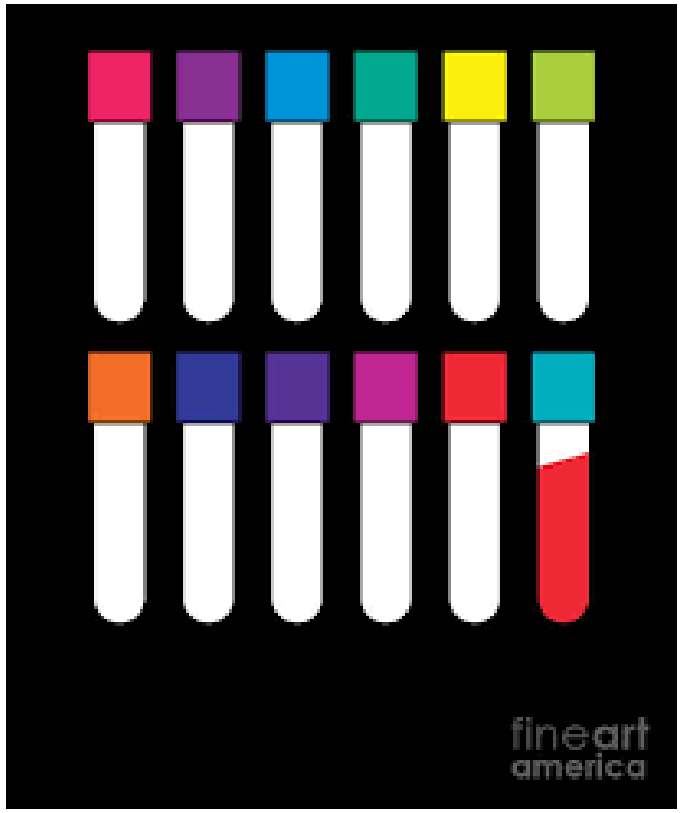
Julia Samsa, MBA, BSN, RN
Cleveland Clinic Foundation
Dept. of Radiation Oncology
9500 Euclid Ave CA6
Cleveland, OH 44195
Phone: (216) 444-7926
E-Mail: samsaj@ccf.org

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

RESEARCH SPECIMENS

- Many studies don't have a separate Lab Manual. Your protocol should indicate how to order kits & specimen processing instructions. They sometimes also have additional forms in the protocol that may need to be completed. Sometimes this is in an appendix.
- If they do have a lab manual, or equivalent, it may be in CTSU under "protocol documents".
- Sometimes, the requisition "paperwork" can only be retrieved in the specimen tracking system. You can't necessarily access this content until the day of the visit because it won't let you enter future dates/times. This can be a burden if you need to ship same day as collection.



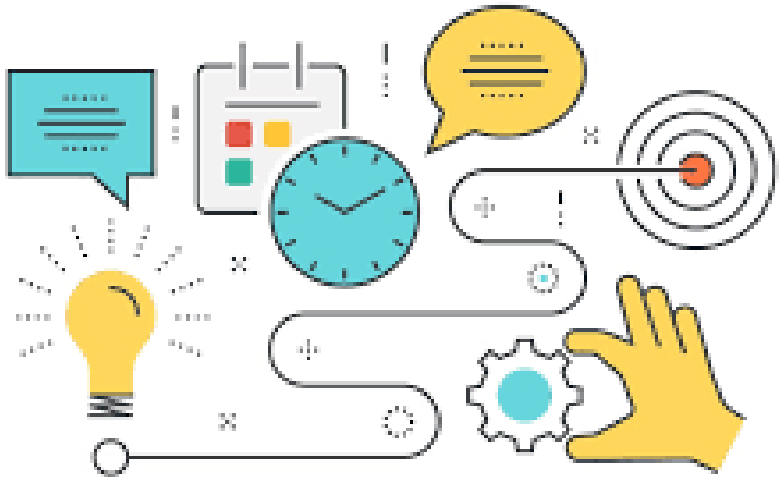
SPECIMEN TRACKING SYSTEMS

- Several cooperative group studies use specimen tracking systems (STS)

- BIOMS (Alliance)
- ECOG STS
- SWOG STS
- ETCTN (historically used RAVE, but recently switched to “Theradex Specimen Tracking System”)

RESEARCH SPECIMENS

- You may need to complete training in order to complete specimen tracking. Check protocol for details.
- OCR: Katie Fox & cGMP don't have access to the STS, so the CRC is responsible for filling in all of that content.
- CRC needs to pay attention to the protocol guidelines re: processing, shipment, and shipping destinations. This can get confusing, especially when there are multiple tests run on one sample.
- Look at the form in advance if possible to determine which questions they'll ask (such as draw time, processing time, freeze time). Ensure you have a way to have this clearly documented.



RESEARCH SPECIMENS

This type of table is often the best resource for determining information about specimens. There is additional content elsewhere in the protocol for processing.

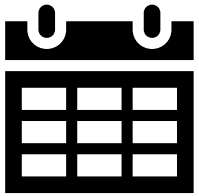
C2D1		
Dose Escalation and Dose expansion: Pre, 0.5, 1, 1.5, 2, 3, 4, 6, and 8h[4]	• 3-4 mL EDTA blood processed for plasma and frozen at each time point (mandatory)	Cancer Pharmacokinetics and Pharmacodynamics Facility, UPMC Hillman Cancer Center
Dose Expansion Only	• 20 mL blood in Streck cfDNA tubes (mandatory)	EET Biobank

These tables seem to be standard for ETCTN, but not other groups

This type of table is typically more confusing than helpful.

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
		CLIA: N	mutations and copy number alterations associated with response, resistance and adaptation.		treatment Dose Expansion only: C2D1 Time of progression	 M M	mickey.williams@nih.gov
3	Circulating Tumor DNA (ctDNA)	ULP-WGS CLIA: N	Exploratory Assessment of mutations and copy number alterations associated with response, resistance and adaptation.	Plasma from Blood in Streck cfDNA Tube	Dose Escalation and Dose Expansion: Pre-treatment Dose Expansion only: C2D1 Time of progression	 M M M	Center for Cancer Genomics, Dana-Farber Cancer Center (DFCI) And The Genomics Platform, Broad Institute of MIT and Harvard Brian D. Crompton, MD BrianD_Crompton@DFCI.HARVARD.EDU
4	Banking		Exploratory Banking for future undecided testing	Plasma from blood in Streck	Dose Expansion Only: at 1st	O	N/A

INVESTIGATIONAL PHARMACY CONSIDERATIONS



- We don't have drug supply on hand for NCI studies. Team needs to allot an extra 2 business days after enrollment to allow time for ordering and delivery of drug.
  - Ex: Drug ordered by 2pm EST on a Wednesday will likely arrive mid-day on Thursday. Therefore, the earliest a patient could likely be treated is Friday.

- IDS is required to return drug (or destroy) within 90 days after an NCI study closes, or when the last patient is treated, whichever is later. They rely on CRCs to update them when studies close, and/or when the last patient is finished treatment.
  - If you've already told IDS that the study closed to enrollment, but still have a patient on treatment, you'll need to send them an update when that patient finishes treatment.

ADVERSE EVENTS

MANAGING ADVERSE EVENTS

- Adverse events are handled similarly to most studies, with some quirks.
  - Abnormal labs reported as AEs
  - SPEER/CAEPR
  - SAE reporting
  - Solicited AEs

ABNORMAL LABS AS AES

- The different cooperative groups have different guidelines about whether abnormal labs that are NCS need to be reported as AEs. The following slides provide some detail regarding this topic.
- NCI guidelines say the following: "After the baseline assessment, all abnormal laboratory values determined to be of *clinical significance* based on the physician's assessment are to be reported as AEs on the appropriate CRF." (Source: DCP Baseline and Adverse Event Reporting Guidelines, 10/25/2021).
- We've also seen other guidelines suggesting that only abnormal labs that are related to specific drugs should be reported as AEs.
- In general- we recommend that you follow your specific protocols guidelines and guidance from your study contacts.
- These are NCI guidelines that are helpful, but sometimes contradict specific protocols.
  - Adverse Events/CTCAE | CTEP
    - See link for "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD and DCP INDs and IDEs (August 30, 2024)

ABNORMAL LABS AS AES: ETCTN

ETCTN:

> Description: This form documents the presence of Adverse Events during the course of treatment. All adverse events, regardless of severity or relationship to treatment, must be reported. Grade 2 or higher lab abnormalities should be reported both in the Lab Results and AE CRFs. Prior to completing this form, please ensure Course Initiation form is completed.

However, our current ETCTN auditor (as of 2024), has suggested that if we receive guidance from the study chair that contradicts the above statement, he would follow that guidance.

Source: Theradex CTMS Rave User Guide

Version 2.2

Referenced from Medidata Rave

ABNORMAL LABS AS AES: NRG

NRG reporting

2. Laboratory Test Values and Vital Signs

Laboratory abnormalities and changes in vital signs (outside of reference range) are considered adverse events if they result in discontinuation or interruption of study treatment, are clinically significant and require therapeutic medical intervention, meet protocol specific criteria (see toxicity management in protocol) and/or if the investigator considers them to be adverse events. Laboratory values and vital signs that meet the criteria for a serious adverse event (SAE) must be reported in an expedited manner.

- Laboratory values and vital signs that are clearly attributable to another adverse event do not require discrete reporting (e.g. electrolyte disturbances in the context of dehydration, chemistry and hematologic disturbances in the context of sepsis, etc.)

All laboratory test results and vital signs captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs must be documented and reported per expedited reporting procedures.

Source: Guidance for Routine Adverse Event Reporting: Jan 3, 2023

NRG > About Us > Statistics and Data Management Center (SDMC) > Data Management Resources

ECOG & ALLIANCE

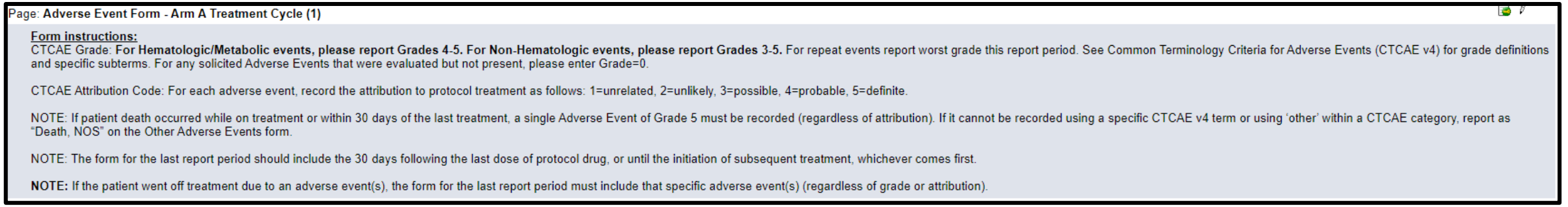
- ECOG & Alliance don't seem to have any formal guidelines that specify whether abnormal labs should be reported as AEs if they're NCS. However, whenever we have emailed representatives from those groups about this question, they have repeatedly confirmed that ALL abnormal labs, regardless of significance need to be reported as AEs.
- For some studies, there may be guidance on the AE form in the EDC that specifies more details on which AEs are reportable.

ABNORMAL LABS AS AES

- If you can't figure out what the protocol requires, here is a template you could use to send to the study chair.
  - *"I am writing you to inquire more about how abnormal labs, vitals, and ECG findings should be reported as AEs for *** study. The protocol does not seem to specify if we should report all abnormal findings as adverse events, regardless of attribution or clinical significance. NCI guidelines indicate, "After the baseline assessment, all abnormal laboratory values determined to be of clinical significance based on the physician's assessment are to be reported as AEs on the appropriate CRF." (Source: DCP Baseline and Adverse Event Reporting Guidelines, 10/25/2021). Could you please specify what is required for this protocol? Reporting all abnormal labs & vitals as AEs requires an immense amount of effort from CRCs, data coordinators and physicians. Most of our pharmaceutical sponsored studies do have language indicating to only report abnormal labs as AEs if the event is considered clinically significant, especially for drugs that have a well-documented risk profile."*

ADVERSE EVENT REPORTING

- Keep in mind that most cooperative group studies use cycle-by-cycle AE logs. This can be much trickier to maintain. Some of them also indicate specific instructions in the EDC itself, such as the type/grade of AEs to report. They may also provide guidance such as only reporting the highest grade AE in the cycle.



Page: **Adverse Event Form - Arm A Treatment Cycle (1)**

Form instructions:

CTCAE Grade: **For Hematologic/Metabolic events, please report Grades 4-5. For Non-Hematologic events, please report Grades 3-5.** For repeat events report worst grade this report period. See Common Terminology Criteria for Adverse Events (CTCAE v4) for grade definitions and specific subterms. For any solicited Adverse Events that were evaluated but not present, please enter Grade=0.

CTCAE Attribution Code: For each adverse event, record the attribution to protocol treatment as follows: 1=unrelated, 2=unlikely, 3=possible, 4=probable, 5=definite.

NOTE: If patient death occurred while on treatment or within 30 days of the last treatment, a single Adverse Event of Grade 5 must be recorded (regardless of attribution). If it cannot be recorded using a specific CTCAE v4 term or using 'other' within a CTCAE category, report as "Death, NOS" on the Other Adverse Events form.

NOTE: The form for the last report period should include the 30 days following the last dose of protocol drug, or until the initiation of subsequent treatment, whichever comes first.

NOTE: If the patient went off treatment due to an adverse event(s), the form for the last report period must include that specific adverse event(s) (regardless of grade or attribution).

SPEER/CAEPR

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** generated list of reported AEs associated with an agent currently under an NCI IND. Information contained is compiled from the IB and other documentation.

- **SPEER (Specific Protocol Exceptions to Expedited Reporting):** A subset of AEs within the CAEPR that contains a list of events that are protocol specific exceptions to expedited reporting.

Adverse Events with Possible Relationship to Durvalumab (MEDI4736) (CTCAE 5.0 Term) [n= 3006]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Keratitis[2]	
		Optic nerve disorder	
		Uveitis[2]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		*Abdominal pain (Gr 2)*
		Colitis[2]	
	Diarrhea		*Diarrhea (Gr 2)*
		Gastrointestinal disorders - Other - (gastrointestinal perforation)[2,3]	
	Nausea		*Nausea (Gr 2)*
		Pancreatitis[2]	
	Vomiting		*Vomiting (Gr 2)*
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		*Edema limbs (Gr 2)*
	Fatigue		*Fatigue (Gr 2)*
	Fever		*Fever (Gr 2)*

SPEER/CAEPR

- Remember: the events in the SPEER have to be related to the drug that is associated with the table. In this case, Durvalumab.

- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ONLY be reported expeditiously if the grade being reported **exceeds the grade** listed in the parentheses next to the event.

AE REPORTING

- While you can use a "verbatim term" to report AEs, you will need to have the CTCAE term. (We generally suggest always using CTCAE terms for AEs to simplify the process).
- Many of the EDCs require AEs to be reported per cycle. This can get tedious to track, as compared to one cumulative AE log.
- Most of the Medidata Rave forms will ask a question such as "attribution to study intervention". But, we often have more than 1 intervention. The guidance below is for ETCTN. May need to ask your study contact on a case-by-case basis.

  - When completing data entry for AEs
    - **Investigational agents only** – enter the overall highest attribution
    - **Investigational and commercial agents** – enter the highest attribution for the investigational agent(s)
    - **Commercial agents only** – enter the highest attribution for the commercial agent

DIFFERENT VARIETIES OF ADVERSE EVENTS

- Cooperative group studies have regular AEs, SPEER/CAEPR, SAEs.
- Some of the studies have AESIs (Adverse Events of Special Interest) that are separate than the SPEER/CAEPR.
- Some of the studies also have solicited AES. They are a list of specific AEs that they want you to review at each visit. The protocol doesn't usually specify these, but they're listed in the EDC.
  - Remember- you'll need source to verify the events were evaluated, even if the event hasn't occurred.

SOLICITED AES

- For example, EA5181 had about 30 solicited AEs. For each visit, the CRC had to indicate that the event was reviewed, but typically the event hadn't occurred. In this case, you would say that the event was "evaluated", and the grade is "0".
- You still need to report regular AEs, even if they're not in the list of solicited AEs by adding an additional log line.

#	Verbatim term	Solicited (derived)	*Adverse event term (CTCAE v5.0)	*MedDRA adverse event code (CTCAE v5.0) (derived)	*Adverse event evaluated this cycle?	*Adverse event grade description (first 120 characters)	Adv eve gra descr (fu descri (deri
21	_	☑	Neutrophil count decreased	10029366: Investigations	Yes	(0) None	_
22	_	☑	Heart failure	10019279: Cardiac disorders	Yes	(0) None	_
23	_	☑	Myocardial infarction	10028596: Cardiac disorders	Yes	(0) None	_
24	_	☑	Pericardial effusion	10034474: Cardiac disorders	Yes	(0) None	_
25	_	☑	Ventricular arrhythmia	10047281: Cardiac disorders	Yes	(0) None	_
26	_	☑	Myocarditis	10028606: Cardiac disorders	Yes	(0) None	_
27	_	☑	Chest pain - cardiac	10008481: Cardiac disorders	Yes	(0) None	_
28	_	☑	Atrial fibrillation	10003658: Cardiac disorders	Yes	(0) None	_
29	_	☑	Atrial flutter	10003662: Cardiac disorders	Yes	(0) None	_

SAE REPORTING

- Each protocol will have a table such as the attached image. It will indicate which events need to be reported expeditiously etc. Pay attention to this table!
- Generally, only report 1 ticket per cycle, even if you have multiple SAEs within that cycle.
- We have had audit findings for over and under reporting SAEs, and for delayed reporting. Delayed reporting is generally classified as a "major" finding.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI in CTEP-AERS accessed via Medidata Rave within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour; 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol-specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" – The AE must initially be reported in CTEP-AERS accessed via Medidata Rave within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

SAE REPORTING

- There may be additional guidelines for reporting SAEs in relation to commercial agents.

5.2.10 Expedited Reporting Requirements for Arm B (Step 1) on protocol EA5181

Commercial Agents: Cisplatin, Etoposide, Pemetrexed, Carboplatin, Paclitaxel

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only – Arm B (Step 1). Once it is determined an expedited report is required, immediately report the event in Medidata Rave so a CTEP-AERS report will be initiated with a link to complete it.

Attribution	Grade 4		Grade 5[a]		ECOG-ACRIN and Protocol-Specific Requirements
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely			7 calendar days	7 calendar days	See footnote (b) for special requirements.
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

Add3

a A death occurring while on study treatment or within 30 days of the last dose of study treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

NOTE: A death due to progressive disease should be reported as a Grade 5 "Disease progression" under the System Organ Class (SOC) "General disorder and administration site conditions". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

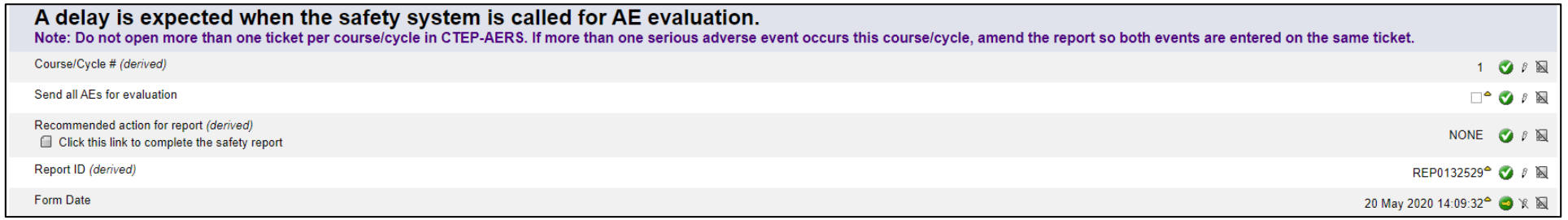
NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported in CTEP-AERS accessed via Medidata Rave within 7 calendar days of learning of the event. For instructions on how to specifically report these events, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

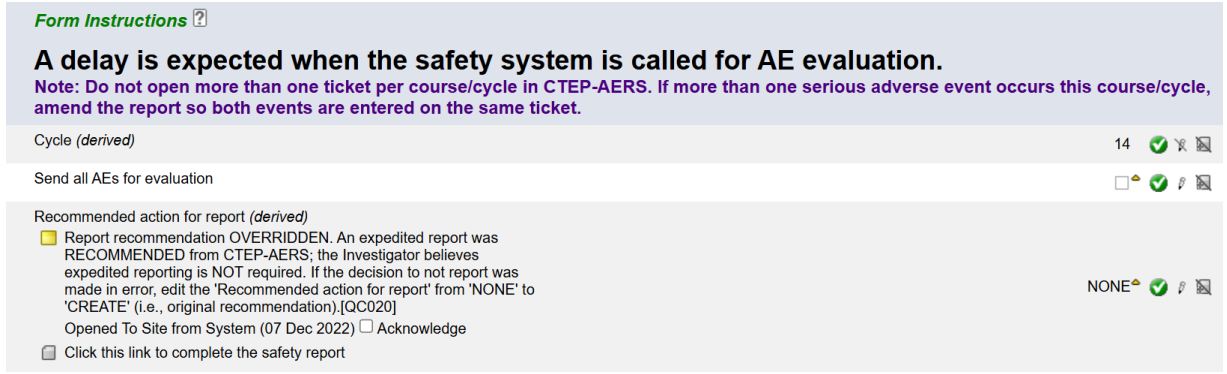
SAE REPORTING

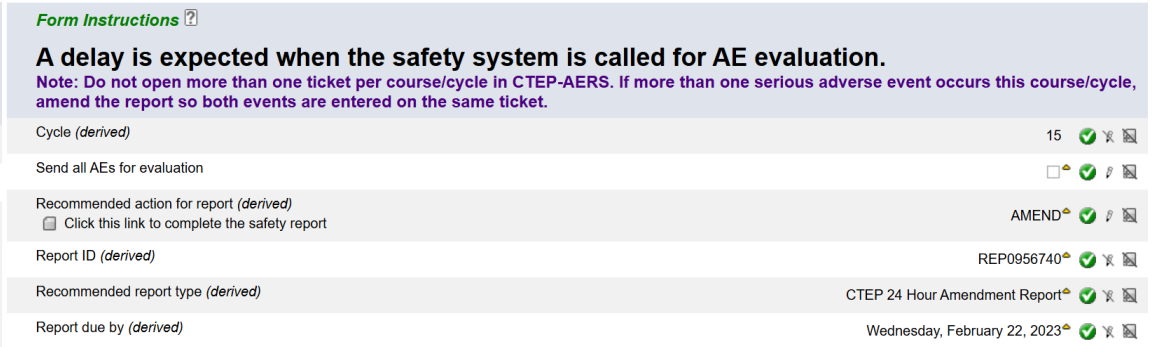
- You will often have to click a button in Medidata in order to "send AEs for evaluation". This will make auto-suggestions about whether any AEs need to be reported as an SAE.
- However, this function is not always accurate, so use it with a grain of salt. You should be able to override the suggestion. It may be helpful to document the reason for override in your deviation/clarification log.
- If an SAE report is indicated, you will generally report it via the link that should populate in the section below.



SAE REPORTING

- The link from Medidata Rave should take you to the CTEP AERs portal.
- You need to get the treating physician (or someone else designated the task to sign AEs per DTL) to sign the SAE report. Ideally, this should occur before the report is finalized. However, if nobody is available to sign, it is more important to submit the report within the deadline, and get the signature later.





SAE REPORTING UPDATE

There was a big update in Aug 2024 affecting SAE reporting for cooperative group studies.

1. **Global Safety Update to Expedited Reporting Requirements for Serious Adverse Events on CTEP-Supported Clinical Trials under IND and/or IDE**

   Background: CTEP expedited reporting requirement tables are provided in all trial protocols to ensure SAEs are reported via CTEP-AERS in compliance with 21 CFR 312.64. Timely reporting ensures that the FDA and all participating investigators are promptly informed of significant new adverse events (AEs) or risks with respect to the drug/device used in the trials as required by 21 CFR 312.50 and 21 CFR 812.

   Reporting Issue/Deficiency: CTEP has been informed by the FDA that the CTEP expedited reporting tables for SAEs are not in complete compliance with regulations. FDA is requiring CTEP to make appropriate modifications in its expedited reporting tables to ensure reporting is compliant with regulations. **The main change needed is instituting the requirement for 24-hour notification to IND/IDE sponsors for ALL SAEs, irrespective of grade/severity, if the AEs meet any of the SAE criterion defined in FDA regulations, followed by a completed expedited report in 5 or 10 calendar days.**

   Corrective Action & Implementation Plan: To update the SAE expedited reporting tables in **all** CTEP-supported clinical trials with and IND/IDE (regardless of the IND/IDE sponsor organization), CTEP will be making a Global Safety Update to expedited reporting via its electronic reporting system (CTEP-AERS) on the evening of **August 30, 2024**, bringing expedited reporting for all trials into regulatory compliance. This Global Safety Update will be made outside of a protocol amendment consistent with federal regulations (45 CFR 46.108 (a)(3) (iii) and 21 CFR.56 108 (a) (4)) as the change is necessary to eliminate apparent immediate hazards to patients by delayed safety reporting of SAEs.

SAE REPORTING UPDATE

Current *vs* Revised: Phase 1 and Early Phase 2 Study Tables

Current: Phase 1 and Early Phase 2 Studies

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An AE is considered serious if it results in **ANY** of the following outcomes:
1) Death
2) A life-threatening AE
3) An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SAEs that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.
Expedited AE reporting timelines are defined as:
- "24-Hour; 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.
Effective Date: May 5, 2011

NIH NATIONAL CANCER INSTITUTE

Revision: Phase 1 and Early Phase 2 Studies

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An AE is considered serious if it results in **ANY** of the following outcomes:
1) Death
2) A life-threatening AE
3) An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SAEs that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-2 Timeframes	Grade 3-5 Timeframes
24-Hour notification, 10 calendar days	24-Hour notification, 5 calendar days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.
Expedited AE reporting timelines are defined as:
- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notifications are required for all SAEs followed by a complete report
- Within 5 calendar days for Grade 3-5 SAEs
- Within 10 calendar days for Grade 1-2 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

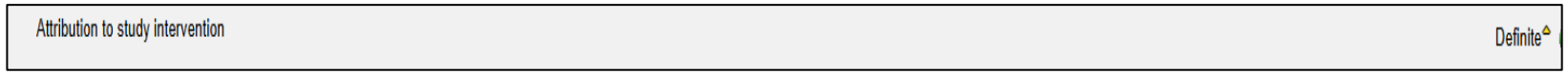
Effective Date: August 30, 2024

TIPS FOR INTERNAL AE LOG

- Even if your EDC just says "attribution to study intervention" and only has 1 option, we recommend having a column or individual response for attribution to each intervention. It can be confusing for the doctors to guess which intervention you're referring to when they fill in AE tables.

EA5181 (IRB 200159) Subject ID: 123456: Toxicity Table, CTCAE v5.0: (reviewed 3/23/22)

Adverse Event	Grade	Start Date	Stop Date	Relation to Cis	Related to Pem	Related to Durva	Related to RT	Action w/ IP	Class
Cough	2	10/20/21	3/22/22	Unrelated	Unrelated	NA	Possible	None	NA
Fatigue	1	9/30/21		Probable	Probable	NA	Possible	None	NA
Dyspnea (worsening)	1	10/5/21		Unlikely	Unlikely	NA	Unlikely	None	NA
Pneumonitis	2	1/12/22	3/23/22	Unrelated	Unrelated	Probable	Definite	D/C from study treatment	NA



TIPS FOR INTERNAL AE LOG: SOLICITED AE DOCUMENTATION

- For OCR: Please document solicited AEs in Epic (unless it's an older study, in which case, use whatever the team has been using to support consistency).
- Note- for any solicited AEs that were considered AEs, they should be on the AE log as well.

Give pill diary/collect pill diary		
Collect Solicited AE's		
A022004 Solicited Adverse Events		
Arm 1 evaluate at baseline and day 1 of each cycle		
	Y	N
Rash maculo-papular	☐	☐
Fatigue	☐	☐
Diarrhea	☐	☐
Vomiting	☐	☐
Elevated creatinine	☐	☐
Optional Studies		

Y	N	SOLICITED AE's
☐	☐	Hypothyroidism
☐	☐	Abdominal pain
☐	☐	Constipation
☐	☐	Nausea
☐	☐	Fatigue, tiredness, or lack of energy
☐	☐	Decreased appetite (anorexia)
☐	☐	Cough (medical HX)
☐	☐	Shortness of breath (dyspnea)
☐	☐	Fever
☐	☐	Urinary tract infection
☐	☐	Blood bilirubin increased
☐	☐	Neutrophil count decreased
☐	☐	Platelet count decreased
☐	☐	Diarrhea
☐	☐	Vomiting
☐	☐	Numbness or tingling in feet or hands
☐	☐	Heartburn
☐	☐	A rash of the hands or feet that can cause cracking, peeling, redness or pain (palmar-planta erythrodyesthesia syndrome)
☐	☐	Rash
☐	☐	Itchy skin
☐	☐	Mouth or throat sores

*All solicited AE's were assessed on this visit.
*All abnormal lab values reportable by CTCAE vs.5 are documented on AE table.
*Any solicited AE's reported by pt. will be inserted into AE log

TIPS FOR INTERNAL AE LOG: SPEER

- Some people will consolidate the SPEER language into a table so it's easier to review at each visit.
- Consider adding a prompt to your CRC checklist that indicates, "Review SPEER table", or equivalent.

SPEERs

*Report AEs on the SPEER **ONLY IF** they exceed the grade noted in paraentheses next to the AE in the SPEER.*

Adverse Events with Possible Relationship to ZEN003694 (ZEN-3694) (CTCAE v.5)	Specific Protocol Exceptions to Expedited Reporting (SPEER)
Eye Disorders	
Blurred vision	***Blurred vision (Gr 2)***
Eye disorders – Other (visual impairment)[2]	***Eye disorders – Other (visual impairment)[2] (Gr 2)***
Flashing lights[2]	***Flashing lights[2] (Gr 2)***
Photophobia	***Photophobia (Gr 2)***
Gastrointestinal Disorders	
Diarrhea	***Diarrhea (Gr 2)***
Nausea	***Nausea (Gr 2)***
Vomiting	***Vomiting (Gr 2)***
General Disorders and Administration Site Conditions	
Fatigue	***Fatigue (Gr 2)***
Investigations	
Platelet count decreased	***Platelet count decreased (Gr 3)***
Weight loss	***Weight loss (Gr 2)***
Metabolism and Nutrition Disorders	
Anorexia	***Anorexia (Gr 2)***
Nervous Systems Disorders	
Dysgeusia	***Dysgeusia (Gr 2)***

DATA QUIRKS

DATA QUIRKS

- Pay attention to data entry guidelines/windows. Generally, most audit findings at UVA are related to data, rather than true deviations.
- Data entry timelines are generally 2 weeks. Pay attention to emails you receive from data team or QAP that provide a summary of overdue data and queries. Please respond to those emails periodically so QAP knows if people are working on the data.
- If you have a good explanation as to why data are late (for example, the patients visit was delayed due to toxicity), be sure to explain that in your deviation/clarification log. May also want to reach out to study contact for guidance.

DATA QUIRKS

- You won't have regular monitoring visits, so periodically CRCs don't realize they're doing something wrong until months or years later.
- Cooperative groups require CRCs/data coordinators to be highly engaged and intrinsically motivated. There isn't an infrastructure in place to keep CRCs/Data coordinators accountable other than infrequent monitoring visits.
- You won't necessarily have a CRA or study contact who contacts you regularly and engages with the site consistently. CRC needs to be proactive, not reactive!
- Pay attention to the protocol guidelines about who to contact re: data management questions.

DEVIATIONS

- FYI- if the protocol doesn't specify a window, typical NCI guidance is that if the procedure is completed more than 10% out of the protocol-specified time, then it's considered a deviation.
- For example: if the protocol indicates drug administration must occur over 60 minutes, and the drug administration was 66 minutes, this may be considered a deviation.

UPLOADING SOURCE DOCUMENTATION

- Some groups will request you to upload specific source documents to the EDC, or sometimes in CTSU. Follow their instructions about what type of identifiers need to be included.
- The documentation must still be redacted!
- If you need to send patient information outside of UVA, remember to send it securely.
- (In general, regardless of the type of trial, all source documents should have some way to identify who the patient is).

Form instructions:
When uploading any type of source documentation please double check to ensure the patient's name and any identifiers, except initials and the patient's ECOG-ACRIN number, have been redacted.

TRIAD (TRANSFER OF IMAGES AND DATA)

- Some studies require image upload using TRIAD.
- https://www.irocqa.org/Resources/TRIAD
- Typically, you upload the images differently compared to other studies, because TRIAD deidentifies the images for you.

  They may also require you to submit radiation plan information in TRIAD.

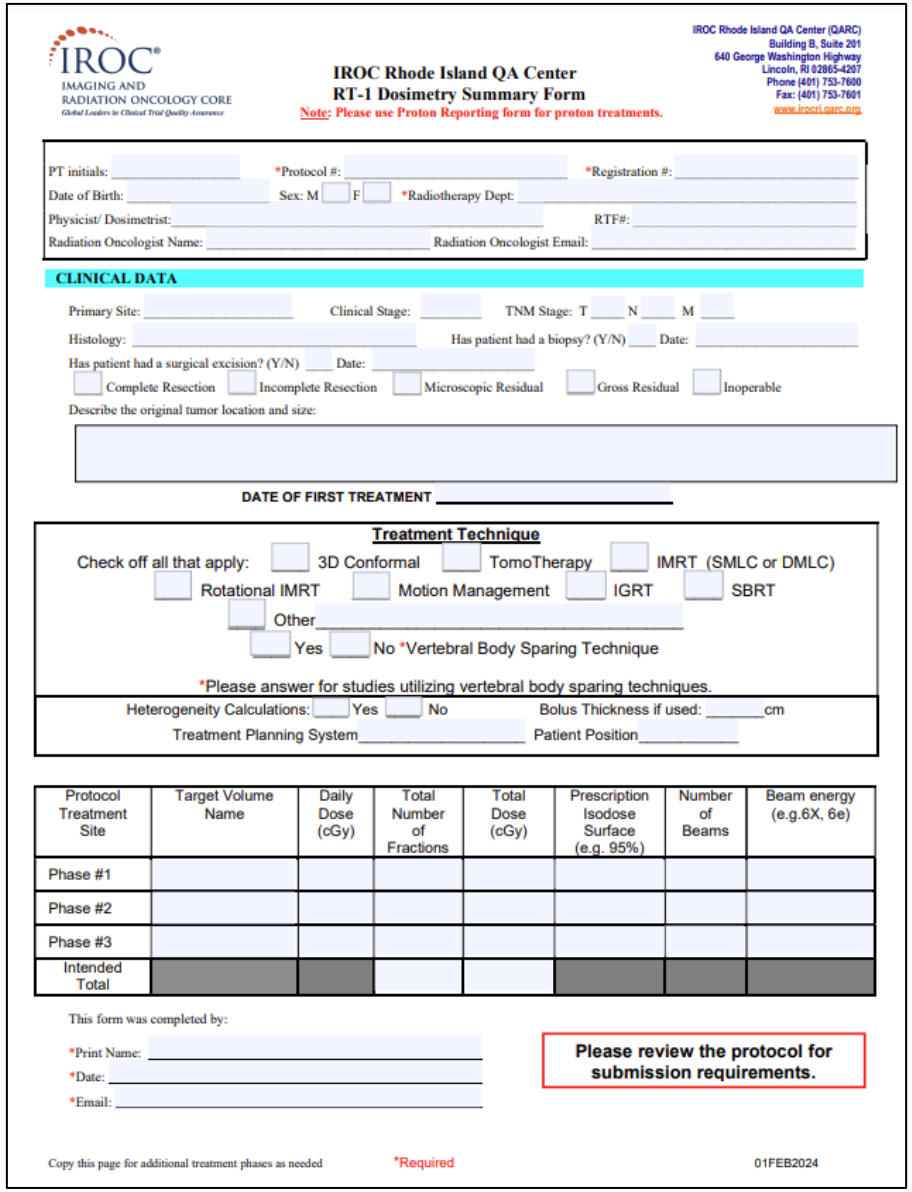
TRIAD

- You won't receive a confirmation that images were uploaded, so we suggest you take screenshots to prove that images were uploaded. Particularly helpful for an FDA audit where the auditor wouldn't have an easy way to verify image submission.

	Subjec...	Timep...	Submissio...	Site	Site#	Trial	Trial#	Enrolling Site	Study ...	Study ...	Images	Accessi...	Validation	Attac...	Add ...	Status
+	VA009-...	12 Mon...	8/17/2022	Univers...	VA009	Limited ...	NRG-LU...	VA009 - Universi...		7/26/2022		0	NA	View (0)	Add	Submitted
+	VA009-...	12 Mon...	8/17/2022	Univers...	VA009	Limited ...	NRG-LU...	VA009 - Universi...		7/26/2022		0	NA	View (0)	Add	Submitted
+	VA009-...	12 Mon...	8/17/2022	Univers...	VA009	Limited ...	NRG-LU...	VA009 - Universi...		7/26/2022		0	NA	View (0)	Add	Submitted

RADIATION

- For studies that include a radiation component, you will often be asked to fill in the "RT-1" form before the patient can be treated with RT. This is a dosimetry information form (related to how much RT is absorbed).
- You may also be asked to submit an "RT-2" form after the RT is completed.
- https://www.qarc.org/qarcforms.htm
- Krishni Wijesooriya is the radiation physicist at UVA who can assist with this process. Typically she wants the CRC to fill in the top box and she'll fill in the rest.



IROC
IMAGING AND RADIATION ONCOLOGY CORE
Global Leaders in Clinical Trial Quality Assurance

IROC Rhode Island QA Center (QARC)
Building B, Suite 201
640 George Washington Highway
Lincoln, RI 02865-4207
Phone (401) 753-7600
Fax: (401) 753-7601
www.irocri.qarc.org

IROC Rhode Island QA Center
RT-1 Dosimetry Summary Form
Note: Please use Proton Reporting form for proton treatments.

PT initials: _____ *Protocol #: _____ *Registration #: _____
Date of Birth: _____ Sex: M ☐ F ☐ *Radiotherapy Dept: _____
Physicist/ Dosimetrist: _____ RTF#: _____
Radiation Oncologist Name: _____ Radiation Oncologist Email: _____

CLINICAL DATA

Primary Site: _____ Clinical Stage: _____ TNM Stage: T ____ N ____ M ____
Histology: _____ Has patient had a biopsy? (Y/N) ____ Date: _____
Has patient had a surgical excision? (Y/N) ____ Date: _____
☐ Complete Resection ☐ Incomplete Resection ☐ Microscopic Residual ☐ Gross Residual ☐ Inoperable
Describe the original tumor location and size:

DATE OF FIRST TREATMENT _____

Treatment Technique

Check off all that apply: ☐ 3D Conformal ☐ TomoTherapy ☐ IMRT (SMLC or DMLC)
☐ Rotational IMRT ☐ Motion Management ☐ IGRT ☐ SBRT
☐ Other _____
☐ Yes ☐ No *Vertebral Body Sparing Technique
*Please answer for studies utilizing vertebral body sparing techniques.

Heterogeneity Calculations: ☐ Yes ☐ No Bolus Thickness if used: _____cm
Treatment Planning System_____ Patient Position_____

Protocol Treatment Site	Target Volume Name	Daily Dose (cGy)	Total Number of Fractions	Total Dose (cGy)	Prescription Isodose Surface (e.g. 95%)	Number of Beams	Beam energy (e.g.6X, 6e)
Phase #1							
Phase #2							
Phase #3							
Intended Total							

This form was completed by:

*Print Name: _____
*Date: _____
*Email: _____

Please review the protocol for submission requirements.

Copy this page for additional treatment phases as needed *Required 01FEB2024

ETCTN SPECIFIC DATA

- If you have ETCTN studies, please consider watching this video. It is a conversation with Austin Hill, our Theradex auditor for ETCTN studies. He talks in extensive detail about data for ETCTN and common issues.

https://www.youtube.com/watch?v=dSWAAV9ASBM&list=PLwM31go5lzn9-xg8L28yZRDa6MPvF48Ti

ETCTN SPECIFIC DATA

- Please use the following smart phrase to access all source document templates you should need for ETCTN studies. These were designed specifically to help reduce confusion/queries and include content in blue font to help the CRC.
- SDTETCTNGENERIC. Ask Maria for access if needed.

Medical history CRF to include:

- Enter diagnoses (e.g., hypertension) not physical exam findings (e.g., distended abdomen) or symptoms (e.g., runny nose, itchy eyes). The cause of the physical findings (e.g., ascites) or symptoms (e.g., seasonal allergies) should be entered
- Enter surgeries not related to the on-study diagnoses
- Enter medication allergies
- This specific form in the EDC is not specifically catering to ongoing, gradable events. Those should be entered in the baseline AE form.

General Medical History Form				
Medical History Term	CTCAE Grade (Optional; not required in EDC)	Onset Date (Optional; not required in EDC)	Ongoing/End Date (Optional; not required in EDC)	Comments (Optional; not required in EDC)

AUDITS

AUDITS

- Kim Underwood and the QAP (Quality Assurance Program) help to prepare for NCI audits & serve as a liaison on audit days between the auditor and CRCs.
- It is expected that a CRC be available to answer questions on days of an audit.
- QAP team will typically receive the list of patients/studies a couple months prior to the audit. They'll complete a review of any pre-identified patients, as much as possible.
- Some auditors will also have "surprise" subjects that they'll select, so anything is fair game. Historically, this hasn't happened for remote audits.
- Typically there will be an audit review meeting w/ the auditor and anyone involved at UVA. They will often review preliminary findings at this time.

AUDITING SCHEDULE

Group	Frequency	Next anticipated audit
ECOG	Every 3 years	Aug 2027
ETCTN	Every January & September (subjects only) May (Full audit)	May 2025
NRG	Every 3 years	Jan 2027
Alliance	Every 3 years	Feb 2027
SWOG	Every 3 years	NA- we haven't registered any patients to SWOG in a while

Any data/source documents that are changed after the patients are announced for an audit can still incur findings, even if the issue was corrected before the audit. But, it is still looked on favorably to update the content if indicated.

AUDITING PREP- SOURCE DOCUMENTS

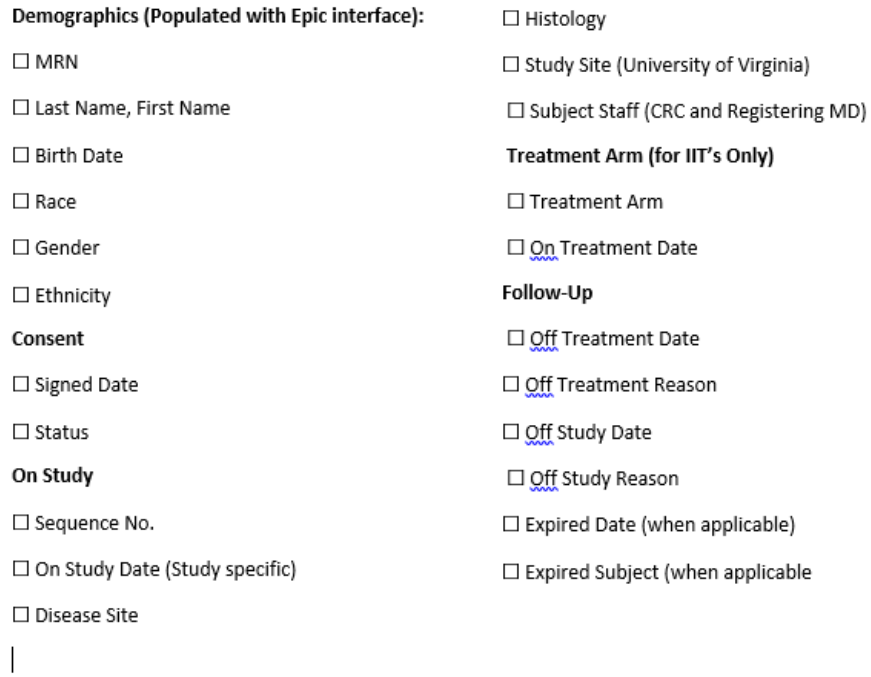
- OCR requirement is that the majority of source are signed within Epic in real-time. Therefore, there shouldn't be much paperwork in a physical binder. Any paperwork may need to be scanned and saved internally as well, including requisition forms etc.
- For other departments: you should follow your departmental practice. However, QAP may request you to scan in all source documentation and save internally depending on the auditors needs. This can vary depending on whether the audit is remote.
- CRC will typically be asked to save all source that aren't available in Epic to the O drive ahead of the audit. QAP will ensure the auditor has access to all of the content via DropBox or other approved method.

AUDIT PREP

- Additional items the auditor may request (this isn't comprehensive):
  - Source document ID form (or equivalent)
  - Deviation/clarification log (or equivalent)
  - Consolidated list of study visits per patient
- FYI- Auditor can request documentation that is not explicitly required in FDA/GCP guidelines. CRCs should strive to go above and beyond the explicit FDA guidelines.
- QAP completes 100% review of Medidata for the patients in an NCI audit. They may request changes to be made.
- Audit trails for any source signed in DocuSign are required to be saved.

AUDIT PREP

- QAP often uses OnCore to provide auditors with patient lists.
  - CRC is responsible for updating OnCore with ALL required fields.
  - The required fields are listed in the attached image.



Demographics (Populated with Epic interface):

☐ MRN

☐ Last Name, First Name

☐ Birth Date

☐ Race

☐ Gender

☐ Ethnicity

Consent

☐ Signed Date

☐ Status

On Study

☐ Sequence No.

☐ On Study Date (Study specific)

☐ Disease Site

☐ Histology

☐ Study Site (University of Virginia)

☐ Subject Staff (CRC and Registering MD)

Treatment Arm (for IIT's Only)

☐ Treatment Arm

☐ On Treatment Date

Follow-Up

☐ Off Treatment Date

☐ Off Treatment Reason

☐ Off Study Date

☐ Off Study Reason

☐ Expired Date (when applicable)

☐ Expired Subject (when applicable

AUDIT PREP: KEYS FOR SUCCESS

Organized Source Documentation

- Physical Binder is organized
- Electronic binder is organized
- Source materials signed in real-time
- Deviation/clarification log is up-to-date.
- Anything/everything related to this subject in Epic etc. is fair game for them to review.
- All source materials are signed/dated by the relevant personnel.

Clean & Up-to-Date Data

- Check for any overdue data.
- QAP to review data when possible.
- Ensure all data are entered. There could be data that haven't been entered but the EDC hasn't flagged the form.

Communication

- Respond to QAP team promptly, even if you haven't completed everything.
- Remember- the QAP suggestions are meant to be helpful.
- If they ask you to update something that you/PI don't think needs to be updated, share that with QAP.

POTENTIAL REPERCUSSIONS OF A BAD AUDIT

- Increases the frequency of audits. This has happened at UVA multiple times. We need to maintain a high enough score for each audit.
- Can lose our ability to enroll patients to the cooperative group's studies.
- Can tarnish our reputation.
- We are all affected by other CRCs at UVA. So, if another group at UVA performs poorly during an audit, that can impact us as well.
- Physician can lose their ability to conduct research, or potentially lose their license, if there was exceptionally problematic findings.

CORRECTIVE AND PREVENTATIVE ACTION

- A detailed account of what occurred
- A summary of the investigation and root cause analysis
- A description of the root cause
- A list of Corrective and Preventive Actions and the plan for implementing them
- Signatures of the Principal Investigator or Sub-I, Research Coordinator, Quality Assurance Manager and other key people involved. The signature requirement varies depending on the study.

POST-AUDIT

- Auditor will correspond w/ QAP about findings and any action items required. Usually this occurs approx. 6 weeks after the audit.
- QAP will facilitate CAPAs. They'll reach out to CRCs to verify.
- CRC/PI should ensure that any CAPAs that are used are realistic/sustainable. They should also ensure they're following previous CAPASs.
- The auditor makes a preliminary determination if the finding is major or minor. The CTMB can overrule the auditor's suggestion and make changes per their guidelines.

AUDIT FINDINGS SUMMARY (EXCLUDING ETCTN)

UVA Major Audit Cycle Findings	2017/2018	2020/2021	2024
Total Major Deficiencies	8	15	18
Total Lesser Deficiencies	17	22	29
Total Subjects Audited	36	26	30
Major Deficiencies by category			
ICF	0	3	8
Eligibility	3	3	2
Treatment	1	0	3
Disease Outcome/Response	2	1	0
Adverse Event	0	5	0
General Data Management (GDM)	2	3	5

Source of tables: Taylor Durham, Fall 2024.

AUDIT FINDINGS SUMMARY FOR ETCTN

ETCTN Audit Findings by year	2017	2018	2019	2020	2021	2022	2023	2024
Total Major Deficiencies	0	4	7	16	7	12	2	5
Total Lesser Deficiencies	5	0	24	11	22	16	4	5
Total Subjects Audited	3	10	18	16	26	18	8	12
Major Deficiencies by category								
ICF	0	0	2	2	2	1	0	0
Eligibility	0	0	1	0	0	1	0	1
Treatment	0	1	1	7	1	2	0	0
Disease Outcome/Response	0	0	0	0	0	0	0	0
Adverse Event	0	2	2	2	1	1	0	0
GDM	0	1	1	5	3	7	2	4

QUESTIONS?

- OCR Clinical Research Educators:
  - Maria Davenport
  - Michal Ande
- QA & Data Manager:
  - Kim Underwood

ACTIVITY CODE

Activity Code: 27051

Instructions for claiming credits/contact hours can be found here.