Clinical Trials Registration

OHSU Knight Cancer Institute
Oregon Clinical and Translational Research Institute

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What is the purpose of registration?

- Fulfill ethical obligations to participants and the research community
- Provides information to potential participant and referring clinicians
- Reduce publication bias
- Help editors and others understand the context of study results
- Promote more efficient allocation of research funds
- Help IRBs determine the appropriateness of a research study (ClinicalTrials.gov)

Why do we register trials?

- Because we have to!
  - Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801) - it is the law!
  - International Committee of Medical Journal Editors (ICMJE) – you want to publish
  - Centers for Medicare and Medicaid Services (CMS) Billing Rule – you want to have Medicare coverage for your trial
  - NIH requires registration

What happens if you don't register?

- FDAAA 801 establishes penalties including civil monetary penalties and, for federally funded studies, the withholding of federal grant funds **AND**
- You may not get Medicare reimbursement for clinical services provided during a clinical trial **AND**
- You may not be able to publish your result **AND**
- You may not be able to get future grants

What studies need to be registered?

- International Committee of Medical Journal Editors (ICMJE) definition

  "Any research project that prospectively assigns people or a group of people to an intervention, with or without current comparison or control groups, to study the cause-and-effect relationship between a health-related intervention and a health outcome (including phase I)."

Who is responsible for registration?

- Responsible Party https://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf
  - Sponsor of the clinical trial as defined by 21 CFR 50.3 (IND/IDE Holder)
  - The Principal Investigator if the PI is conducting the trial, has access to the and control over the data from the trial, has rights to publish the results, and has the ability to meet the requirements

When do I register my study?

- Before the first participant is enrolled – ICMJE
- Within 21 days of enrolling the first participant FDAAA
- You can register it before you have final IRB approval but you must list it as “Not yet recruiting”

How do I register my study?

- If your study is cancer related – the Knight Cancer Institute will register your study under their institutional account (more on this later)
  - This is any study that indicates it involves cancer in your IRB Initial Review Questionnaire
- All other OHSU investigators …

How do I register my study?

- Apply for an **individual** Protocol Registration and Results System (PRS) Account
  - OHSU IRB Help Sheet - ClinicalTrials.gov Registration Requirements http://www.ohsu.edu/xd/about/services/integrity/policies/upload/Clinical-Trials-ClinicalTrials-gov-Registration-Requirements-Help-Sheet.pdf
  - This document has field by field instructions for the PRS account request information
- Once you have your PRS account #, you can update or modify your registration through eCRIS or directly in clinicaltrials.gov

eCRIS

OREGON HEALTH & SCIENCE UNIVERSITY

eCRIS electronic Clinical Research Information System

You can use eCRIS to help register your study

- You must indicate
  - This in an interventional trial (question in eIRB)
  - PI had a significant role in the design of the study and
  - OHSU PI is the lead PI on OHSU only or a multicenter trials (eCRIS)

1. * **Did OHSU Principal Investigator (PI) have significant role in design of study?:**

(●) Yes ( ) No Clear

If Yes, please specify

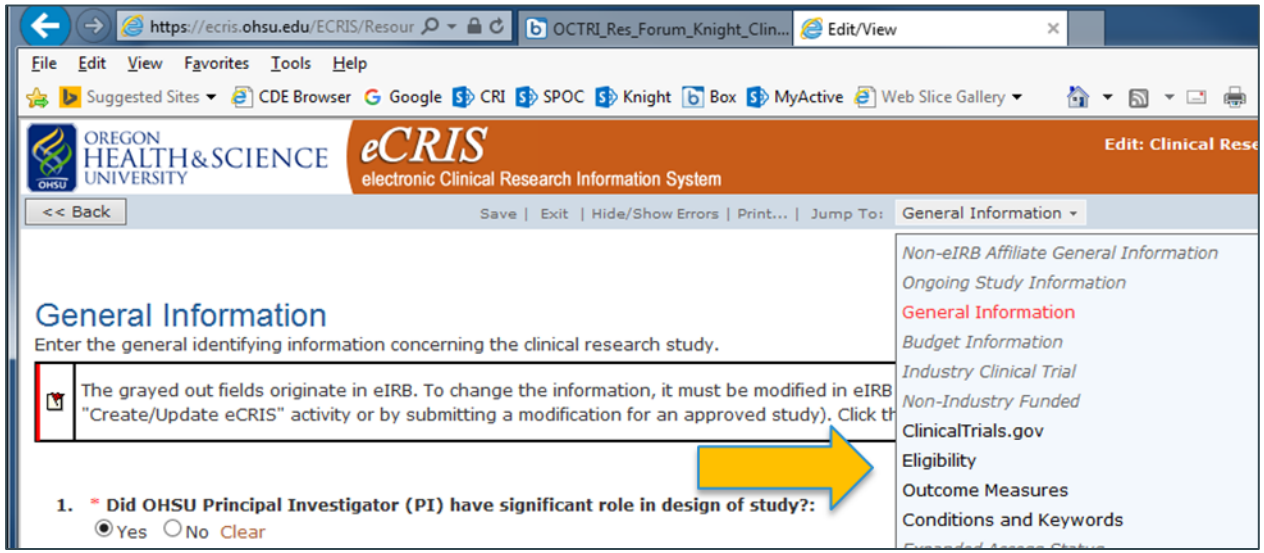
- [x] OHSU PI is Lead PI (e.g. "Sponsor" of IND/IDE Study, lead PI of multicenter study)
- [ ] PI is on the study specific Data & Safety Monitoring Board/Data Monitoring Committee
- [ ] PI is on the protocol design committee
- [x] PI authored protocol
- [x] Other

If Other, specify role:

PI is one of the medical monitors

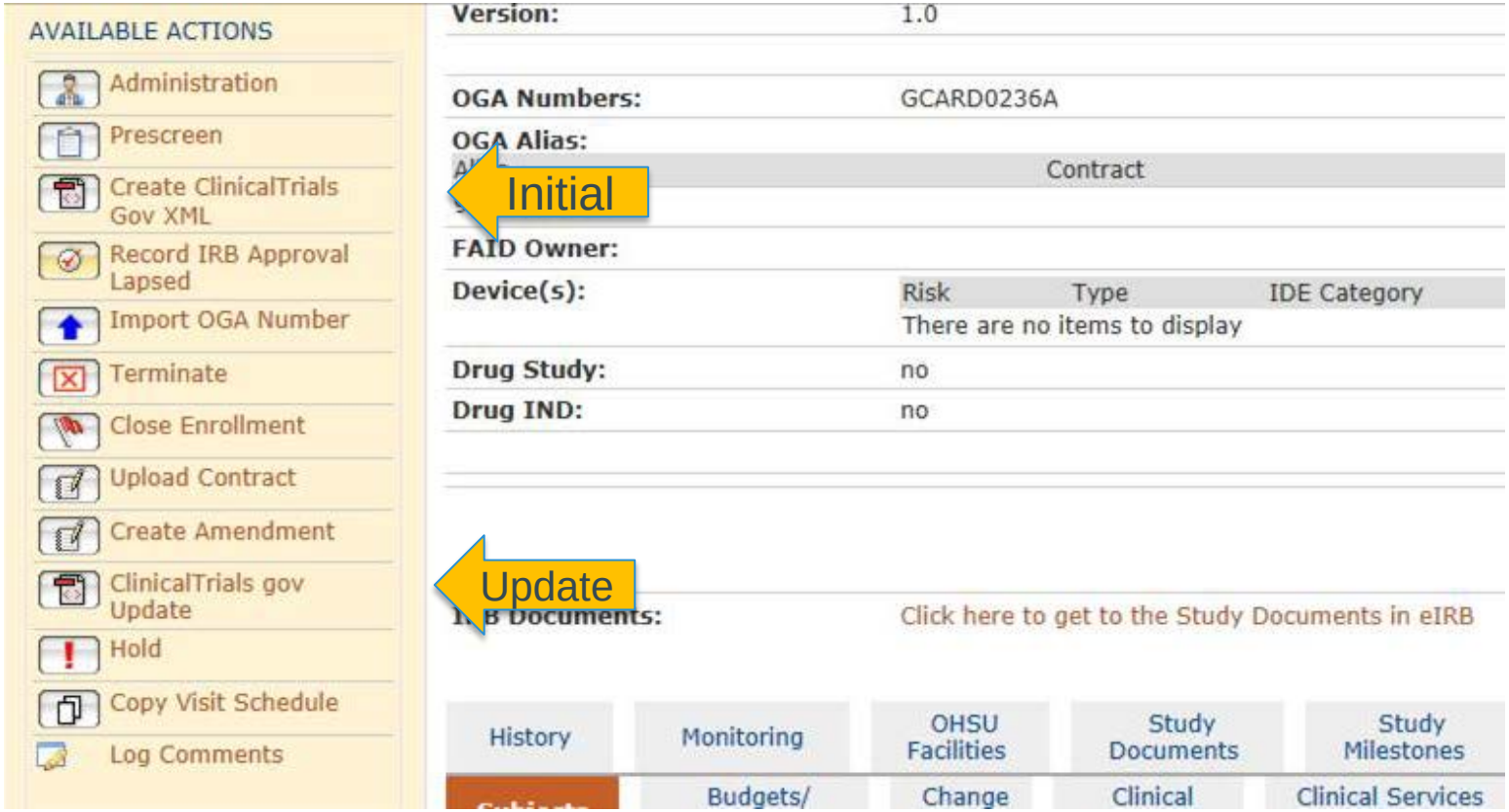
eCRIS Clinicaltrials.gov cont.

- You will be asked to fill out smart forms in eCRIS that you can export to and XML file

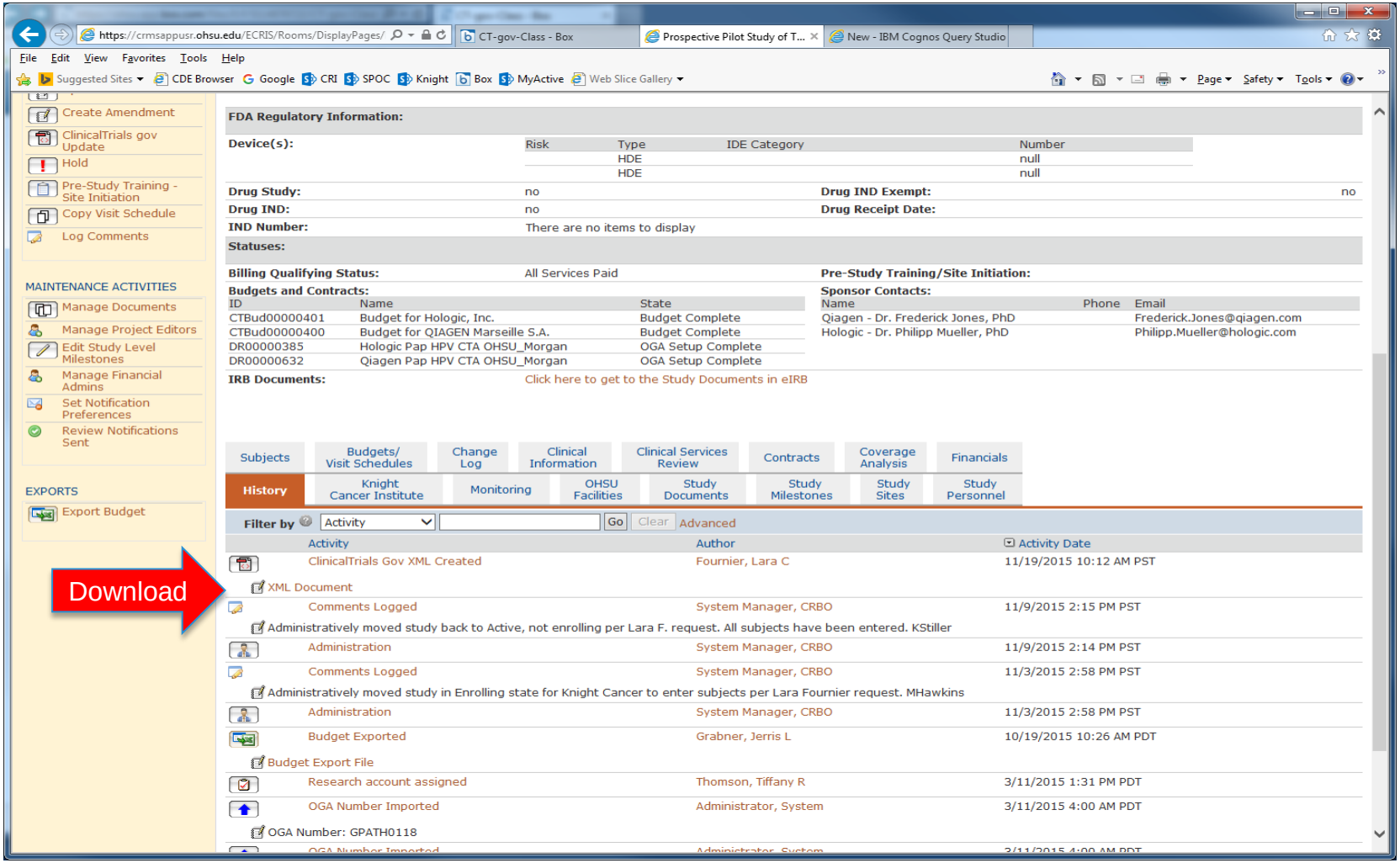


- You can upload the XML file into clinicaltrials.gov for initial registration and for updates
- http://www.ohsu.edu/xd/research/centers-institutes/octri/loader.cfm?csModule=security/getfile&pageid=2308573

eCRIS Actions – Create XML

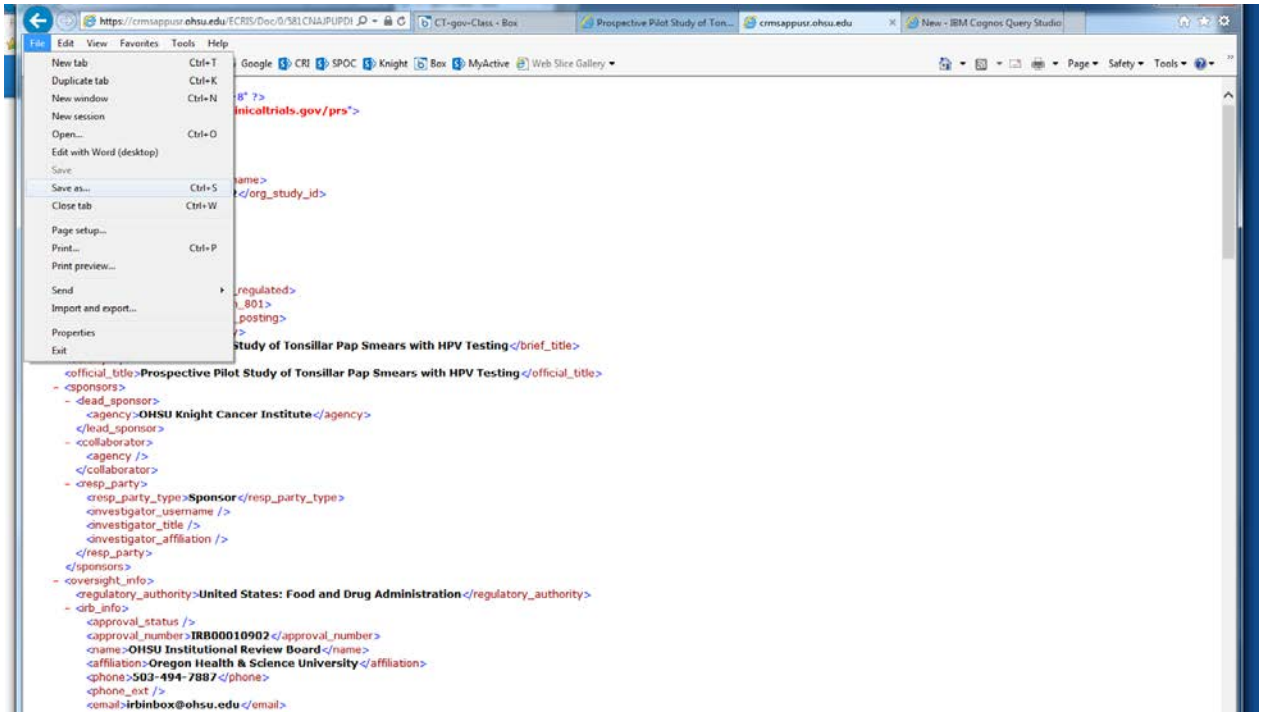


Download XML file from eCRIS



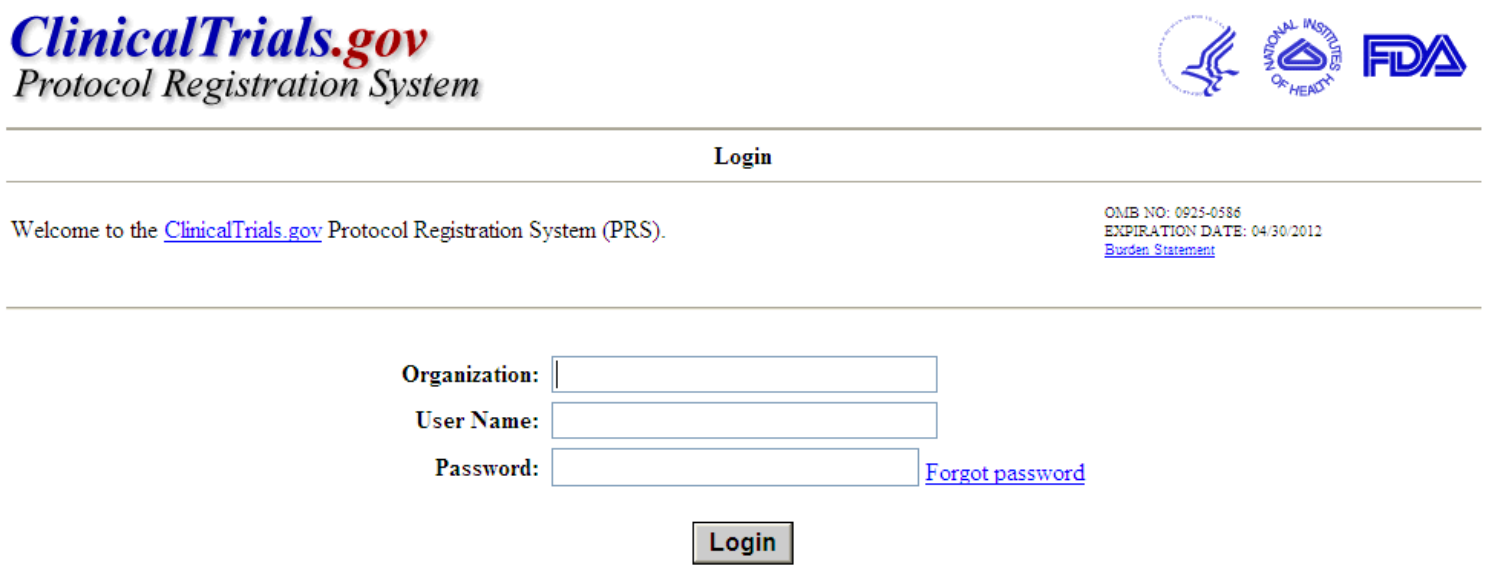
XML File

- Save the file where you can find it so you can upload it in Clinicaltrials.gov
- The file will always be available in eCRIS



Registration Steps

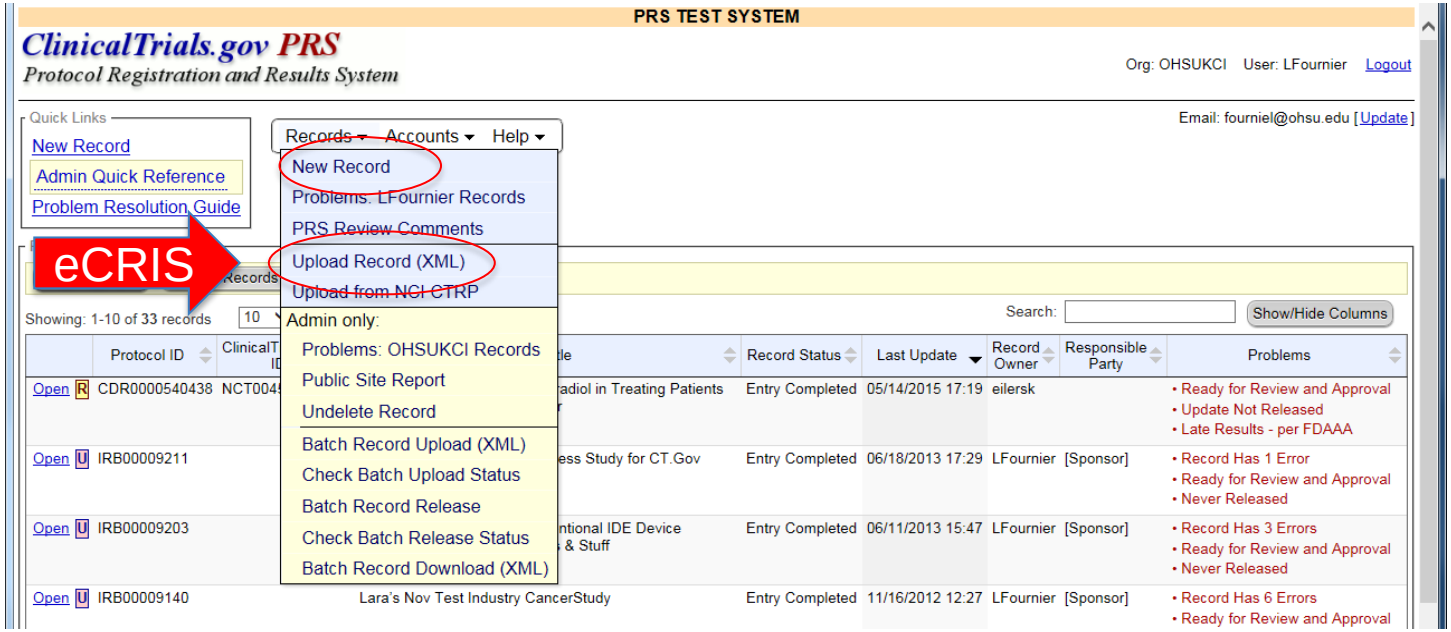
- Go to the ClinicalTrials.gov Login Page https://register.clinicaltrials.gov/



Clinicaltrials.gov Menu

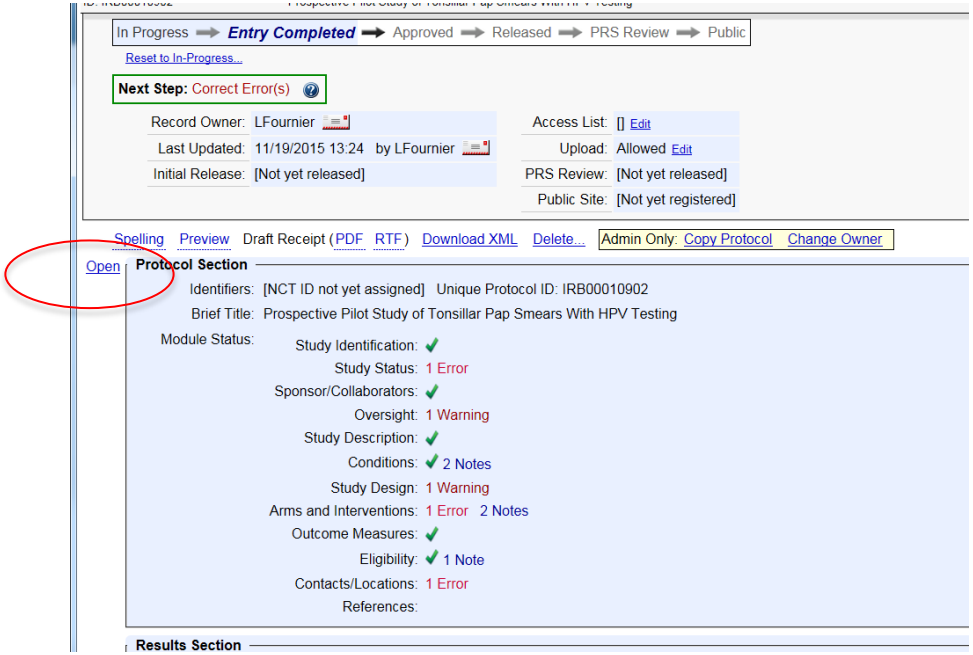
Check out the "Quick Links" section for the Problem Resolution Guide
To create a new protocol record, click "New Record"

To upload your XML export from eCRIS click the Upload Record (XML). There is an XML Upload User Guide (available when you are logged in). Do not attempt to upload other file types. Including XML files created from Microsoft Office using the "Save As" function



After XML Upload

- Click Open and address any errors or warnings
- Errors will prevent you from moving forward
- Warning alert you to additional requirements that may apply to your study



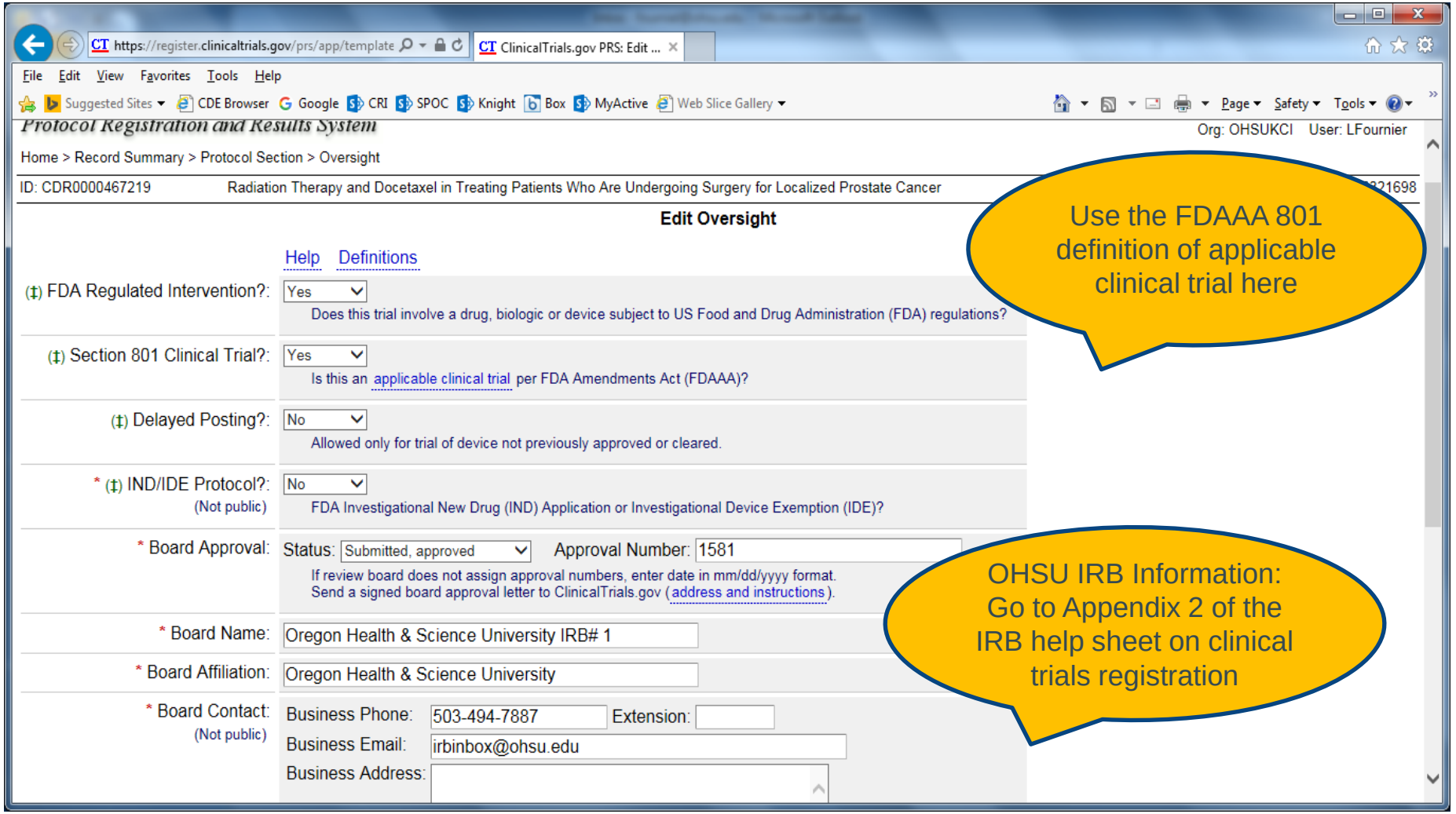
Registration Cont.

Click on any underlined word in the left column for the definition and # of characters allowed

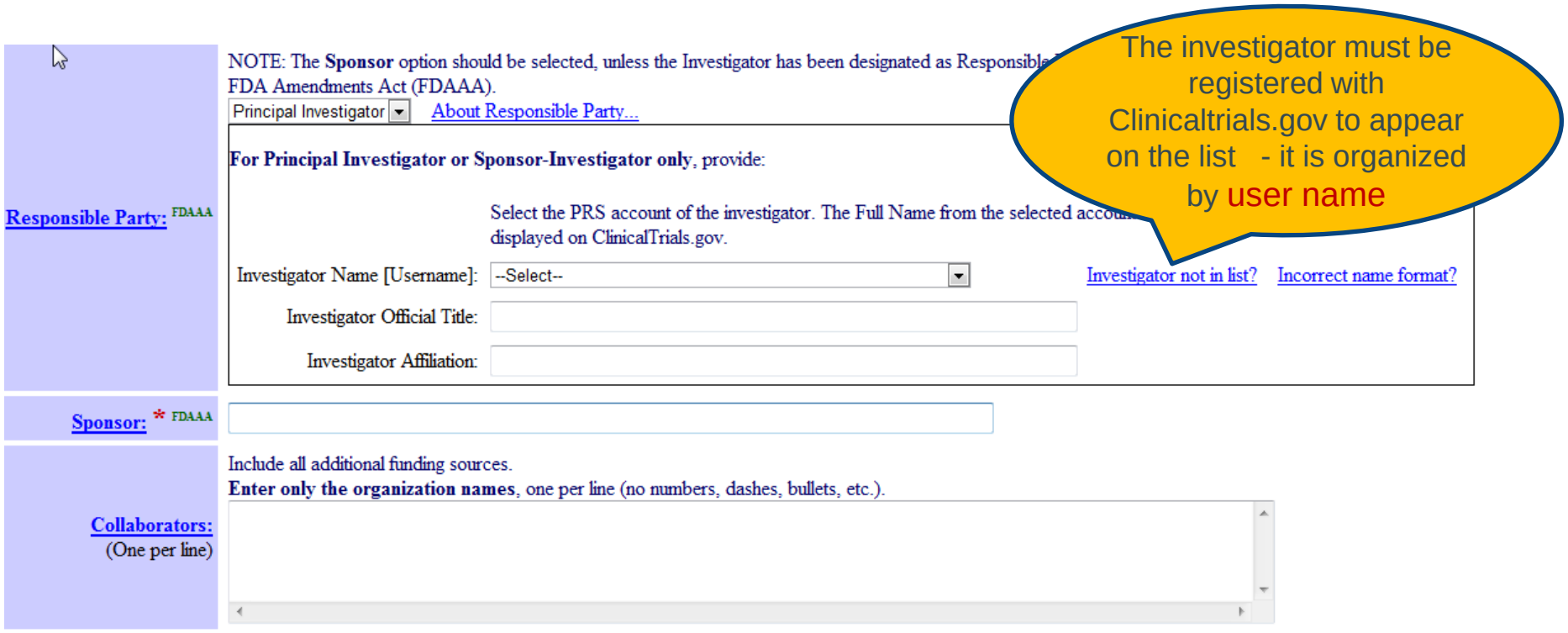
Unique Protocol ID: * FDAAA	Enter sponsoring organization's unique identifier.
Brief Title: * FDAAA (Special characters)	Use lay language. Example: Safety Study of Recombinant Vaccinia Virus Vaccine to Treat Prostate Cancer
Acronym:	If there is an acronym or abbreviation used to identify this study, enter it here.
Official Title:	Example: Phase 1 Study of Recombinant Vaccinia Virus That Expresses Prostate Specific Antigen in Metastatic Adenocarcinoma of the Prostate
Study Type: * FDAAA	○ Interventional ○ Observational ○ Expanded Access About expanded access records
FDA Regulated Intervention? (FDAAA)	Indicate whether this trial includes an intervention subject to US Food and Drug Administration regulations. --Select--
IND/IDE Protocol? * (FDAAA)	Indicate whether the protocol is subject to US Food and Drug Administration regulations, under an Investigational New Drug (IND) Application or Investigational Device Exemption (IDE). --Select--

*** = Required**

IRB Approval



Responsible Party Designation



The investigator must be registered with Clinicaltrials.gov to appear on the list - it is organized by user name

Responsible Party vs. Record Owner

- **The Responsible Party (RP)** is responsible for registering their study
- **Record Owner (RO)** can be anyone with an account; the record is stored in RO's account.
- **TIPS:**
  - If the RP is the Principle Investigator (PI), it may be easiest if the PI is also the RO.
  - The RO can use the "access list" to grant additional users access to the specific record for editing purposes (e.g. if the PI is the RO, he/she can provide access to the study coordinator by selecting the study coordinator from the access list.)

Registration Tips

Summary should be in lay language

Abbreviations must be spelled out the first time they are used

The overall recruiting status must match the location recruiting status

Start date and completion dates are required
Keep your primary completion date up to date or you could end up on the “Problem List”

Change the verification date to the current month and year. You are supposed to update every 6 months.

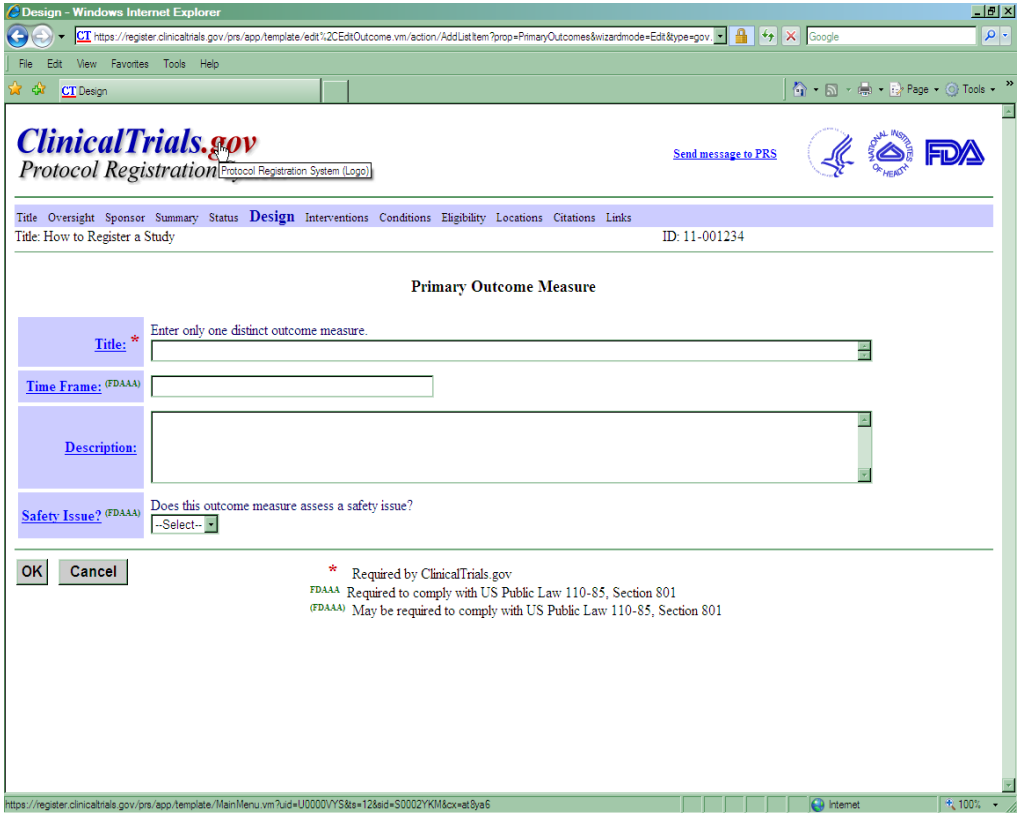
Brief Summary:	How to enter a study record onto ClinicalTrials.gov
Detailed Description:	

NOTE: Detailed Description: data not entered.

Record Verification Date:	July 2012
Overall Status:	Not yet recruiting
Study Start Date:	August 2012
Primary Completion Date:	September 2013 [Anticipated]
Study Completion Date:	September 2013 [Anticipated]

Entering Outcome Measures

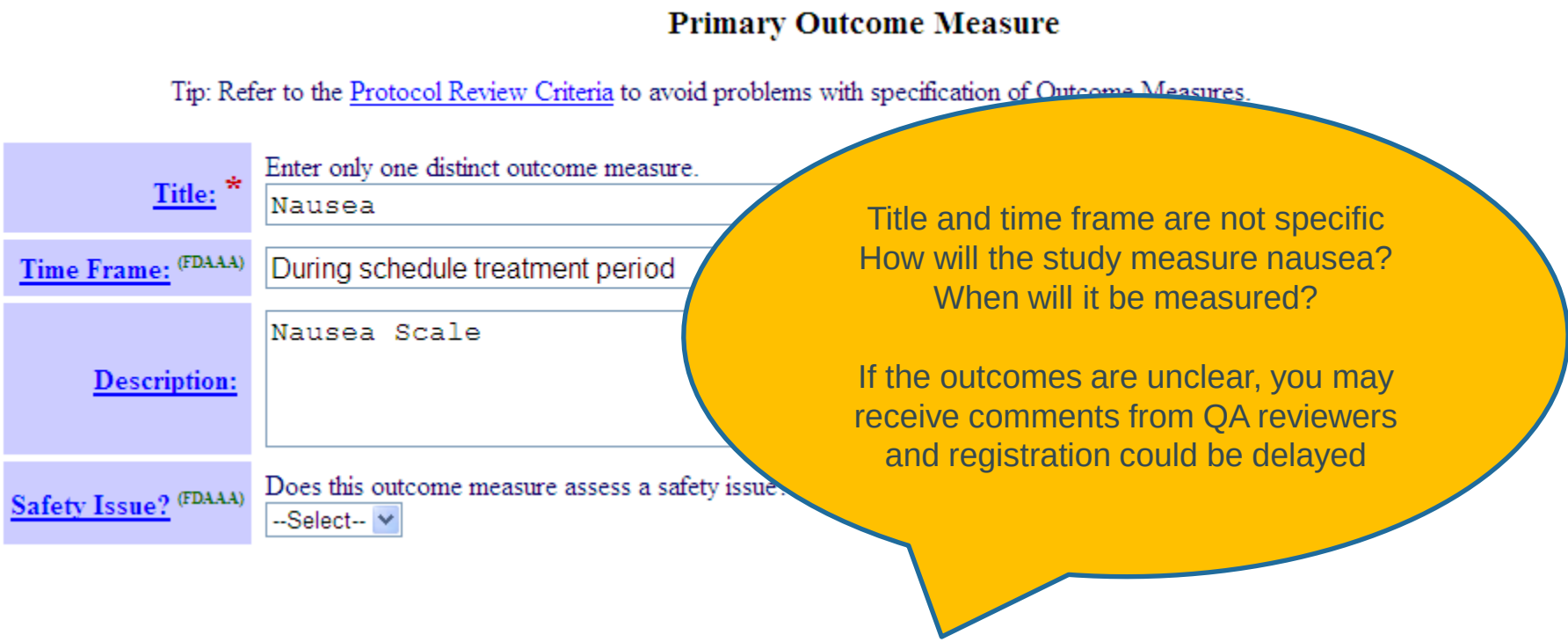
- Be specific
- Outcome title – include the name of the specific measure. Avoid using verbs – do not put "To determine…"
- Time Frame – use a specific metric (hours, weeks, years) do not use "until the end of the study" or "death"
- Description – specify what will be measured not why. If the outcome measure is a scale, provide the range and what a low or high score means
- Is the outcome measure assessing safety



Objectives vs Outcomes

- This Outcomes information will pull into the results module later so define them well
- Objectives are not the same as outcomes
  - Object example = evaluate safety and tolerability
  - Outcome = Grade 3 and higher adverse events measured at 24 months

What is wrong with this primary outcome?



A Well Defined Primary Outcome

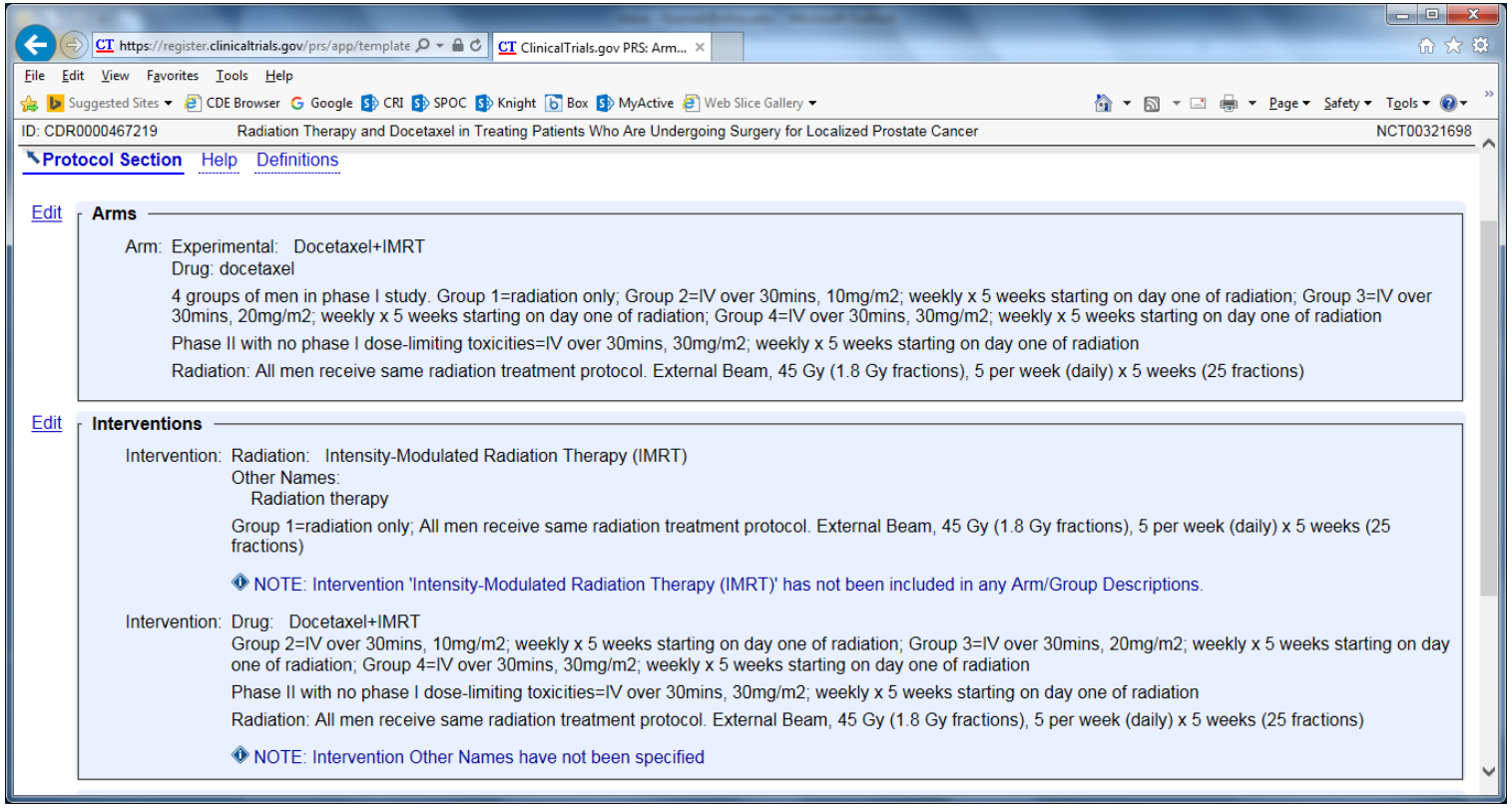
Primary Outcome Measure

Tip: Refer to the Protocol Review Criteria to avoid problems with specification of Outcome Measures.

Title: *	Enter only one distinct outcome measure. Number of Participants improved on the nausea scale
Time Frame: (FDAAA)	8 weeks
Description:	Nausea scale range: 1 (severe) to 10 (none). Change: score at 8 weeks minus score at baseline. "Improved" = greater than 3 point difference in nausea scale.
Safety Issue? (FDAAA)	Does this outcome measure assess a safety issue? No

Entering Arms/ Interventions

If the same intervention is used in multiple arms, enter the information once and then use the Cross-Reference section to specify which arm(s) the intervention is associated with



Contact/Location Information

Central Contact

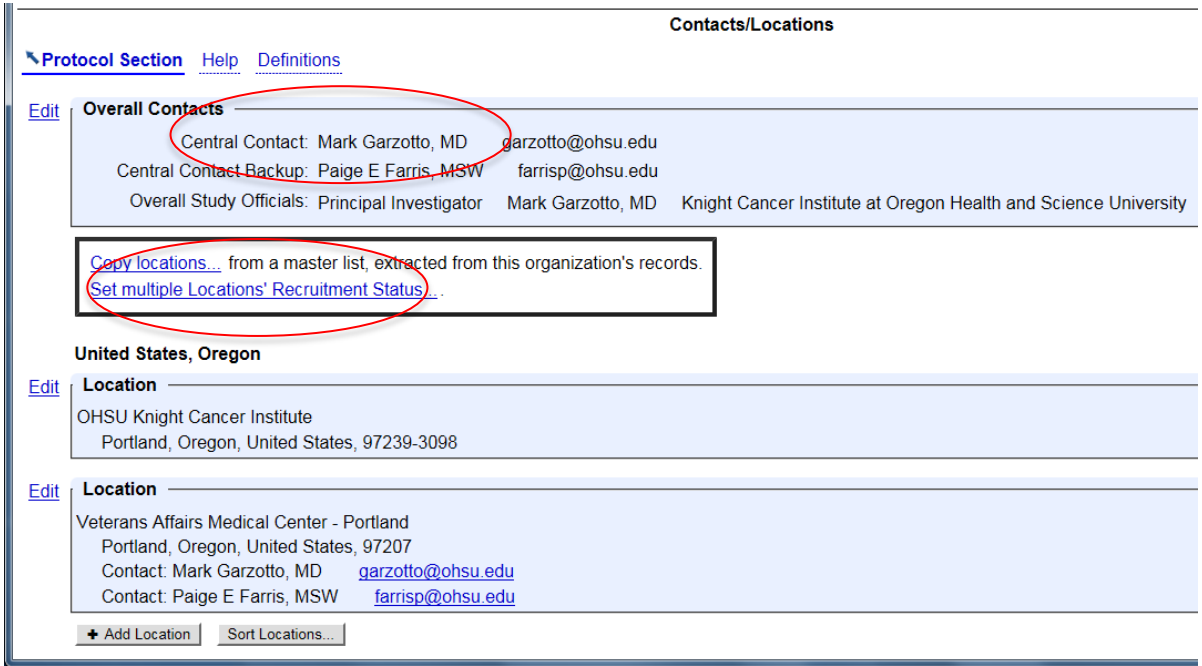
List the person providing centralized recruitment information

Locations

List all study sites (multicenter)

Recruitment status should match overall recruiting status

Keep this up to date and provide complete contact information so that participants and others know who to call



How do I register my study? - Cancer/Oncology Studies

- Go through the OHSU Knight Cancer Institute, Contact ctrp-admin@ohsu.edu with protocol, consent form, IRB approval memo and completed checklist document
- National Cancer Institute abstracts the protocol for you
- The PI will review and approve a trial summary report (TSR)
- It takes NCI staff 10 days to provide the TSR for review
- Once it is approved NCI provides XML format for upload to CT.gov
- The Knight registration staff will do the upload for you
- What is a cancer study? Indicated in IRB IRQ.
  - Studies with focus on cancer or subject population primarily made up of cancer patients.
  - Studies with intent to treat, prevent, diagnose cancer or improve comfort /quality of life of cancer patients. Includes Epidemiologic/Observational/Outcomes/Lab-based studies that assess cancer risk, outcomes or therapy response.

Clinical Trial Registration Process - Cancer/Oncology Studies

- NCI expects all interventional trials that are conducted in NCI-Designated Cancer Centers to be registered
- Knight-sponsored interventional cancer trials are to be registered with CTRP first, before ClinicaTrials.gov
- After CTRP registration, Knight CTRP staff will upload a data file to ClinicalTrials.gov per the Knight SOP

NCI Clinical Trials Reporting Program (CTRP)

- NCI launched a new system to replace PDQ® system - the Clinical Trials Reporting Program (CTRP).
- Fulfills a recommendation made by the NCI Clinical Trials Working Group (CTWG) to the National Cancer Advisory Board.
- The purpose of CTRP is to establish a comprehensive database containing regularly updated information on all NCI-funded clinical trials.

OHSU

Transfer of Study Registration(s) on Cancer/Oncology Studies

- Knight CTRP staff will periodically audit all OHSU-associated studies registered in Clinicaltrials.gov under individual accounts to see if they are cancer-related. When these are discovered, these study records will be transferred to the OHSU Knight Cancer Institute's organizational account:
- **NOTE:** Record transfer does not change level of access, editing or the NCTID (Clinicaltrials.gov ID number). However, if the study originally had the PI as the responsible party, this will be changed to the Knight Cancer Institute so that we can release study records for publication to the Clinicaltrials.gov web site.

OHSU

CTRP Clinical Trial Record Maintenance: Amendments (CTRP requirements)

- Amendments are any change that substantively alters the trial protocol document and require IRB approval
- Clinical trial records are to be amended within **20 business days** of IRB approval of protocol amendment

CTRP Clinical Trial Record Maintenance: Amendments (Knight Process, Pt 1)

1. Per Knight SOP, within five (5) business days after a protocol amendment/modification IRB approval, Knight CTRP staff will gather following items:
   - Amended protocol (clean copy)
   - Change memo detailing the changes to protocol or tracked changes version of protocol
   - IRB approval memo

OHSU

CTRP Clinical Trial Record Maintenance: Amendments (Knight Process, Pt 2)

2. Knight CTRP Staff submit documents to NCI CTRP
3. NCI's CTRP staff provide revised trial summary report (TSR) for review
4. Knight CTRP staff will email TSR to study record owner for review

OHSU

CTRP Clinical Trial Record Maintenance: Amendments (Knight Process, Pt 3)

5. Study staff will note changes to TSR using Word tracked changes and return revised TSR to Knight CTRP Staff at ctrp-admin@ohsu.edu
   - If no response is received within 5 days, it will be assumed TSR is correct
6. Repeat steps 4-6 until TSR is accurate and complete
7. Knight CTRP Staff will finalize amendment with NCI CTRP and upload amended CTRP information to ClinicalTrials.gov

OHSU

CTRP Clinical Trial Record Maintenance: Updates (CTRP Requirements)

- Updates are changes that don't impact the way clinical trial is conducted (e.g. change in PI contact information or change in Anticipated Primary Completion Date)
- At a minimum, updates should be reported every 6 months

OHSU

CTRP Clinical Trial Record Maintenance: Updates (Knight Process, Pt 1)

1. Per Knight SOP, within five (5) business days after a minor change to a clinical trial (e.g. change in Primary Completion Date or trial status), Knight CTRP staff will gather following items:
   - List of all minor changes made to protocol since last amendment
2. Knight CTRP Staff updates trial information in NCI's CTRP
3. NCI's CTRP staff provide revised trial summary report (TSR) for review

OHSU

CTRP Clinical Trial Record Maintenance: Updates (Knight Process, Pt 2)

4. Knight CTRP staff will email TSR to study record owner for review
5. Study staff will submit changes as needed in tracked changes doc to Knight CTRP staff
6. Repeat steps 4-6 until TSR is accurate and complete
7. Updated CTRP information will be uploaded to ClinicalTrials.gov

OHSU

Maintenance- All Responsible Parties

- Update your study records within 30 days a change to any of the following:
  - Changes in recruitment status
    - Not yet recruiting, recruiting, enrolling by invitation, active – not recruiting, completed, suspended, terminated, withdrawn
  - Completion date
  - Changes in contact personnel
  - Every 6 months it is strongly recommended that you verify information is correct
  - At least annually
    - Non substantive protocol amendments (e.g. change to statistical plan)

Frequent Registration Problems

- Who at OHSU registers my trial? Keeps track of my password?
  - You OR
  - The Knight Cancer Institute
- Oops I didn't register my study, now what?
  - Register as soon as possible
- My study doesn't meet the definition of a clinical trial but the journal wants me to register
  - Register as soon as possible
- I registered my study but I can't find it?
  - May not be released yet because of errors – check you email and your spam
  - Missing from cancer.gov notify the Knight registration staff, they can help you
- I received an email from the eIRB telling me I need to register but my study doesn't meet the definition, now what?
  - If you study doesn't meet the ICMJE definition you don't need to register

How to search results

- Allows you to look for results of studies that may not have had publishable results.
- This may help with protocol design and scientific justification
- Go to the Find Studies and click Advanced Search
- Enter your topic area
- Select “Studies with Results” from the study results drop down list
- If studies have results posted the status will state “Has Results”

References and Additional Resources

- Clinicaltrials.gov information https://www.clinicaltrials.gov/ct2/about-site/results
- Questions register@clinicaltrials.gov
- FDAA https://www.clinicaltrials.gov/ct2/manage-recs/fdaaa
- CMS – Mandatory Reporting of NCT #s on Medicare Claims Q&A https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/Downloads/Mandatory-Clinical-Trial-Identifier-Number-QsAs.pdf
- PRS User's Guide XML section (must be logged in to PRS to access) https://register.clinicaltrials.gov/prs/app/template/ReferenceGuide.vm?popup=true&uid=U0000W56&ts=3&cx=-pf1azb#xml
- OHSU Knight Clinical Trial Registration SOPs: CR007, CR013 -
- https://bridge.ohsu.edu/research/knight/policies/SitePages/Home.aspx
- Knight CTRP staff ctrp-admin@ohsu.edu
- OHSU ClinicalTrials.gov IRB Help Sheet: http://www.ohsu.edu/xd/about/services/integrity/policies/upload/Clinical-Trials-ClinicalTrials-gov-Registration-Requirements-Help-Sheet.pdf

Some of the slides were adapted with permission from the work of the Clinical and Translational Science Awards (CTSA) program's Clinical Trials Registration Workgroup of the Regulatory Knowledge Key Function Committee. Original slides available at Harvard Catalyst https://catalyst.harvard.edu/programs/regulatory/clinical-trial-reg.html

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Thank You