

SOP#: RPS-9

**Preparing Protocol Documents for eCTD Submissions
to the FDA**

Version #: 2.0

Next Review Date: 01/2020

Approved Date: 01/2018

Review Interval Period: Biennial

NCI Clinical Director Signature:

POLICY

The CCR Office of Regulatory Affairs (ORA) will submit Investigational New Drug Applications electronically to the FDA's Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER).

PURPOSE

In order to submit documents electronically to CBER and CDER at the FDA, CCR ORA is providing instructions to you, the protocol authors, on the formatting of protocol documents. ORA encourages the use of the Protocol and Informed Consent templates available on the [CCR website](#) and the submission of protocol documents in MS Word format rather than in Portable Document Format (PDF).

FDA requires that the Protocol and Informed Consent documents are submitted as two separate electronic files. Please note that the final MS Word documents when converted to PDF format should be compliant with PDF file requirements specified in FDA guidelines summarized below.

MS Word offers a variety of formatting options and methods; please refer to the user manual for version- specific instructions.

CCR cannot accept MS Word documents that are:

- read-only
- password-protected
- contain macros
- saved with a file extension other than .doc or .docx

RESOURCES

- FDA - Electronic Common Technical Document (eCTD) [webpage](#)
- FDA Portable Document Format Specifications, [Version 4.1](#)

PROCEDURES**Step 1: Font**

The following fonts are allowed in the Word document:

Font Type	Font Name
Serif	Times New Roman
	Times New Roman Italic
	Times New Roman Bold
	Times New Roman Bold Italic
Sans Serif	Arial
	Arial Italic
	Arial Bold
	Arial Bold Italic
Non proportional	Courier New
	Courier New Italic
	Courier New Bold
	Courier New Bold Italic
Other	Symbol
	Zapf Dingbats

- Use font sizes ranging from 9 to 12 points. Times New Roman, 12-point font is recommended for narrative text; point sizes 9-10 are recommended for tables and footnotes. Smaller point sizes should be avoided.
- Use the same font size throughout the document (for example, all text should be in 12-point font). Double check this as sometimes when cutting and pasting the fonts sizes are different.
- The same justification type (either center or left) should be used throughout the document.
- Black is the recommended font color except that blue should be used for all hypertext links or cross-reference links. This includes the Table of Contents, endnotes and cross references to tables, figures, appendices, etc. Avoid light colors since they do not print well on grayscale printers.
- Avoid using image-based graphics as they will not be searchable when converted to PDF. If images are used, they should be high resolution.

Step 2: Page Layout

- Pages should be properly oriented. For example, you should set the page orientation of landscape pages to landscape prior to saving the PDF document in final form to ensure correct page presentation.

- The print area for pages should fit on a sheet of paper that is 8.5"x11" (landscape: 11"x8.5"). Allow a margin of at least 3/4" (preferably 1") on all sides. Header and footer information should not appear within 3/8" from the edge.
- Set tables to a maximum width of 6.5" (landscape: 9").
- Use *Insert Page Number* function to add consecutive page numbers to each document, including appendices. Use Roman numerals (I, II, III, IV, etc.) for the Change Memo/Summary of Changes and Arabic numerals (1, 2, 3, 4) for the document's main content.
- Check that page numbering:
 - Does not collide with text of document
 - Is consecutive (i.e., does not skip numbers or pages within the document)
 - The title pages for the protocol and consent start with page 1.
Note: You are not required to include the page number on the title page as long as the next page starts with 2.
- Ensure that objects, figures, watermarks, etc. do not collide with text of the document or run off the page. All text and figures must be legible

Step 3: Formatting

Set up your Heading levels so that when the document is converted to PDF, bookmarks include:

- Heading Levels 1 (sections 1, 5, 13, etc.) in the protocol
- Heading Levels 2 (sections 1.5, 2.1, 3.2, etc.) in the protocol
- Heading Levels 3 (sections 1.5.1, 2.1.4, etc.) in the protocol
- Major sections of the ICD (Why is this study being done? How long will you be in the study?, etc.)
- Table of Contents
 - Ensure that hyperlinks work for each item and page numbers are correct for each section
 - Ensure all Level 1, 2 and 3 headings/bookmarks are also in the Table of Contents (TOC)
 - Appendices must be in the TOC
- Summary of Changes (if applicable)
- Title page (recommended but not required)
- Schema (recommended but not required)
- Appendices

Ensure when you click on the bookmarks you are taken to the correct section.

Step 4: FDA Submission

- Save all documents for the FDA submission in a separate folder labeled “FDA” that is within the folder for protocol. Create a new subfolder for each submission to the FDA (e.g. Initial submission, Amendment A, Amendment B, etc.). This will ensure that the IND team uses the correct documents for submission.
- All documents should be saved in word format. If an initial submission, just the clean copy should be saved. If an amendment/revision, then saved only the tracked version.
 - Review the document in pdf format (convert from Word using PDFMaker under the ACROBAT tab) to ensure that figures, tables, and references are appropriately linked and labeled
 - Select all and update with F9
 - Do a search for the word “error” and “section 1” to review for sections not appropriately linked
- Create a ticket in JIRA for the IND manager notifying them that the documents are ready for submission to the FDA.

Step 5: Responding to FDA comments

- When responding to FDA comments, you need to provide the clean and tracked protocol, and the response to each FDA comment in a separate document. This is the one time you do not need to create the embedded summary of changes in the protocol or consent document itself.
- Do not add additional changes at this time; only respond to the FDA comments. Additional changes (such as changes in response to the IRB stipulations/recommendations) can be made in a subsequent amendment to the FDA.
- When responding to FDA comments, use the last version of the protocol that was submitted to the FDA. Change the version date to a new version.
- If you have a second set of FDA comments, start with the clean version of the document that was sent in response to the first set of FDA comments. Again, make a new version date.
- Create a separate change memo (different document) with all the changes inclusive from the previous submission to the FDA. Confirm with the IND manager which version was most recently submitted to the FDA.

Step 6: Amendments

Protocol and Consent need to be submitted as separate documents with change memo/summary of change (SOC) embedded within each.

- If the only change to the protocol is the version date, then an SOC embedded within the protocol is not required.

- If there are no changes or the only change to the consent form is the version date, this can be noted in the protocol SOC or consent SOC (i.e., an SOC embedded within the consent is not required if the statement is included in the protocol SOC).
- All changes made in the document must be identified in the SOC; if additional changes have been made that are not identified, or if the changes described in the SOC do not match the changes made in the document, you will need to provide corrected documents.

Hyperlinks must be provided for each change in the SOC. Hyperlinks and Cross-references must be in blue.

Cross references in SOC:

- When you click on a link, it should bring you to the exact section where the change is taking place. If it does not, it needs to go to at least the start of the second heading level (e.g., if the change is in section 2.4.3, the link should take you to at least section 2.4).

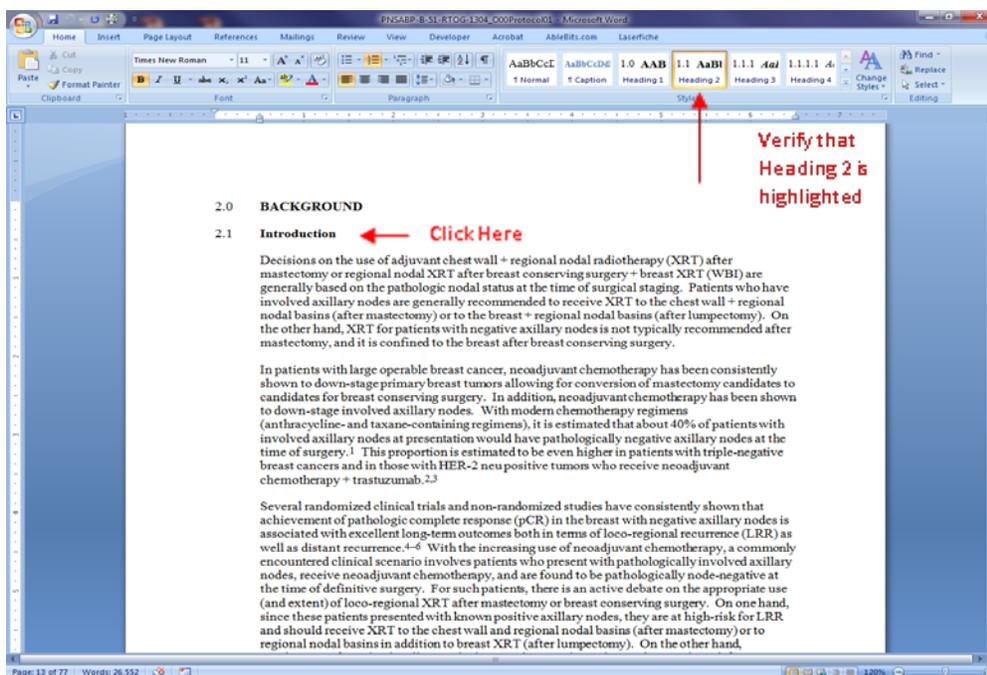
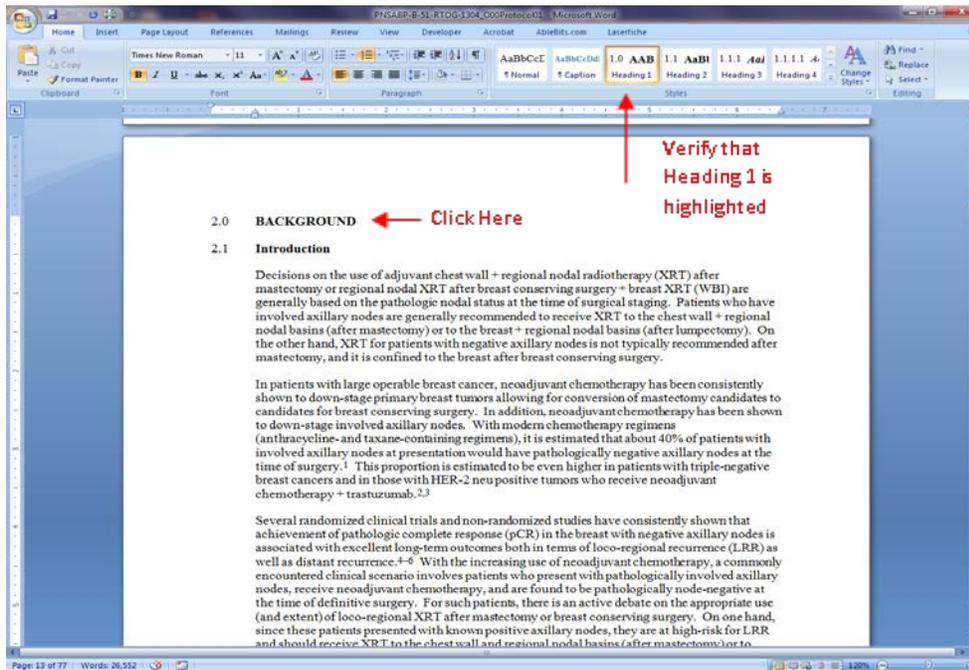
Referenced Sections in SOC:

- The Section Numbers or page numbers for the changes referenced in the SOC must be accurate based on the current clean submission document. For example, the SOC cannot list a change as occurring in section 4.1 if it in fact occurs in section 4.2. Likewise, if the modified section was previously numbered section 4.2, but additions to other parts of the document resulted in it being renumbered to section 4.3, the SOC should list the change as occurring in section 4.3.

Appendix A – Heading Styles

Heading Styles Used for the Document Headings in Word

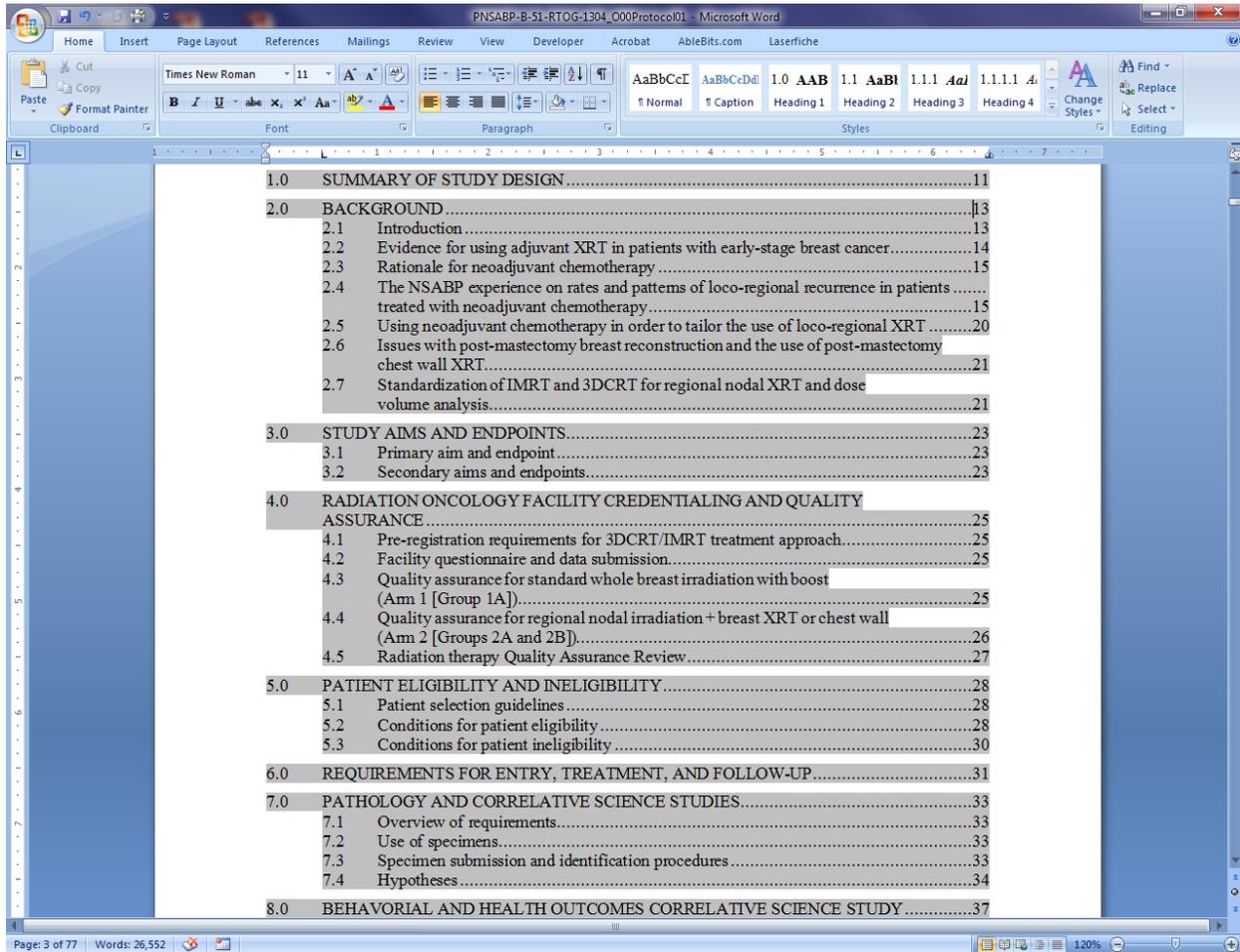
Click on the text of a heading and verify that appropriate Heading Style is highlighted under the Home Tab.



Appendix B - Table of Contents (TOC)

TOC Included and Built Using Word Functions

Right click anywhere in the TOC and the entire table should become highlighted



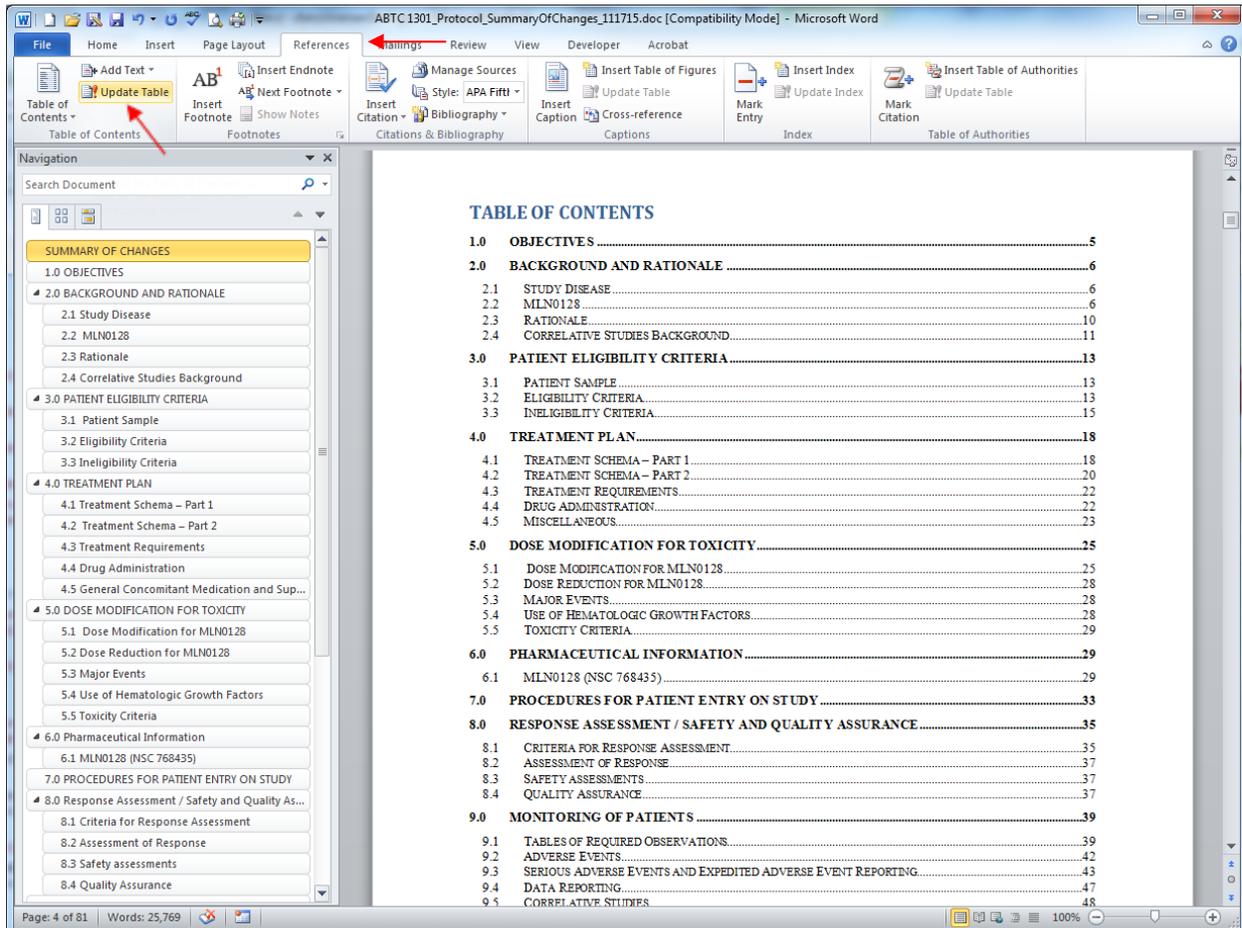
The screenshot shows a Microsoft Word document titled "PNSABP-B-51-RTOG-1304_000Protocol01". The Table of Contents (TOC) is displayed in the main window and is highlighted. The TOC includes the following sections and page numbers:

1.0	SUMMARY OF STUDY DESIGN	11
2.0	BACKGROUND	13
2.1	Introduction	13
2.2	Evidence for using adjuvant XRT in patients with early-stage breast cancer	14
2.3	Rationale for neoadjuvant chemotherapy	15
2.4	The NSABP experience on rates and patterns of loco-regional recurrence in patients treated with neoadjuvant chemotherapy	15
2.5	Using neoadjuvant chemotherapy in order to tailor the use of loco-regional XRT	20
2.6	Issues with post-mastectomy breast reconstruction and the use of post-mastectomy chest wall XRT	21
2.7	Standardization of IMRT and 3DCRT for regional nodal XRT and dose volume analysis	21
3.0	STUDY AIMS AND ENDPOINTS	23
3.1	Primary aim and endpoint	23
3.2	Secondary aims and endpoints	23
4.0	RADIATION ONCOLOGY FACILITY CREDENTIALING AND QUALITY ASSURANCE	25
4.1	Pre-registration requirements for 3DCRT/IMRT treatment approach	25
4.2	Facility questionnaire and data submission	25
4.3	Quality assurance for standard whole breast irradiation with boost (Arm 1 [Group 1A])	25
4.4	Quality assurance for regional nodal irradiation + breast XRT or chest wall (Arm 2 [Groups 2A and 2B])	26
4.5	Radiation therapy Quality Assurance Review	27
5.0	PATIENT ELIGIBILITY AND INELIGIBILITY	28
5.1	Patient selection guidelines	28
5.2	Conditions for patient eligibility	28
5.3	Conditions for patient ineligibility	30
6.0	REQUIREMENTS FOR ENTRY, TREATMENT, AND FOLLOW-UP	31
7.0	PATHOLOGY AND CORRELATIVE SCIENCE STUDIES	33
7.1	Overview of requirements	33
7.2	Use of specimens	33
7.3	Specimen submission and identification procedures	33
7.4	Hypotheses	34
8.0	BEHAVIORAL AND HEALTH OUTCOMES CORRELATIVE SCIENCE STUDY	37

Update TOC with New Headings or Corrected Page Numbers (Word documents only)

If it is noted that page numbers listed in the TOC are not consistent with the actual page numbers in the document, or if heading styles of sections have been corrected in order for section headings to display as bookmarks and in the TOC, then the TOC can be updated to reflect these corrections (if it was built using Word functions).

Click on the References tab and select “Update Table”



A pop-up window will appear. Select whether to “Update page numbers only” (if no heading styles have changed and the update is only meant to correct page numbers) or “Update entire table” (if headings have been updated so that missing sections will be displayed in the TOC; this will also update the page numbers) as appropriate.

