National Cancer Institute (NCI)
Experimental Therapeutics Clinical Trials Network (ETCTN) Guidance

CTEP Submission Requirements

Contents

Introduction

This guidance document was created using CTEP's Protocol Development Resources and the experience of DF/HCC study teams who have submitted ETCTN documents to CTEP. Always refer to the CTEP website for the latest submission requirements. Please contact the CTEP Protocol and Information Office (PIO) at pio@ctep.nci.nih.gov when there are study-specific submission questions.

Project Team Member Applications

The Project Team Member Application (PTMA) Form is provided by CTEP when the PTMA Announcement is released. It often has the CTEP IND Agent field pre-populated with the drug name for the current project team. Investigators must use the most recent version of the form. The form must be submitted via email as a Microsoft Word document or a text-based PDF (created directly from an electronic source as opposed to an image-based scanned file). Supplemental documents such as CVs and Letters of Support should be attached to the submission email as separate documents. The supplemental documents can be Microsoft Word documents, text-based PDFs, or image-based PDFs.

It is unlikely CTEP will request a revised PTMA. It is also unlikely that CTEP will provide comments regarding the PTMA at the time an investigator is invited to take part in the drug project team. If a revised PTMA form is requested or review comments are supplied, the CTEP PIO will provide instructions regarding how the response should be provided.

Letter of Intent

Initial Submission

The Letter of Intent (LOI) Form is available on the CTEP website. CTEP does not routinely send email announcements when the form has been updated so investigators should always download the form directly from the website when preparing a new LOI for submission. The form can be submitted as a Microsoft Word document or text-based PDF. Supplemental documents such as CVs and Letters of Support should be attached to the submission email as separate documents. The supplemental documents can be Microsoft Word documents, text-based PDFs, or image-based PDFs.

Consensus Review

CTEP reviews the LOI and a standard table format (refer to Appendix C for an example) is used when providing the CTEP consensus review comments to the Protocol Chair. The consensus review comments serve as the basis for the Operational Efficiency Working Group (OEWG) teleconference agenda so the Protocol Chair should review the comments prior to the call. It is recommended that the Protocol Chair wait until after the conference call takes place before preparing a formal response to the CTEP consensus review because the comments may change as a result of the conference call discussion.

Conference Call Summary

CTEP provides a Conference Call Summary shortly after the OEWG call. The summary is created using the original consensus review and adding details regarding the conference call decision for those comments that were discussed. The Protocol Chair and other participants on the call must review the summary within the timeframe specified in CTEP's email (usually 48 hours). The Protocol Chair does not need to provide a formal response (i.e., does not need to fill in the sections labeled "**PI Response**") at this time. He or she is simply reviewing the summary to verify the conference call decisions accurately reflect what was discussed on the call. The Protocol Chair or designated study team member can respond to CTEP with comments and/or provide edits to the call summary. This can be done either in the body of an email or by using tracked changes to edit the call summary document directly. If the summary is acceptable, no response to CTEP is required.

The cover letter accompanying the consensus review will specify when a formal response to the LOI comments is expected. It may be required at the time the revised LOI is submitted to CTEP or if a revised LOI is not required, the response is due at the time of initial protocol submission. **The**

conference call summary is considered an amended consensus review and the Protocol Chair must use that document when responding to CTEP.

Responding to CTEP LOI Comments

The Protocol Chair must provide a response in bold directly below each comment in the consensus review. The comments fall into one of the following categories:

1) Comments from CTEP or Pharmaceutical Collaborator requiring a Response: For each of these comments the Protocol Chair should make the suitable revisions or provide the reason in the "**PI Response**" section of the summary of changes for not making the suggested modifications.

2) Recommendations from CTEP or Pharmaceutical Collaborator: These comments are advisory and Protocol Chair is not obligated to make these changes. The "**PI Response**" section should be used to indicate if the changes were made or declined.

The formal response to the LOI comments should be included as a separate email attachment (i.e., not embedded at the beginning of the LOI or Protocol document as a summary of changes). Refer to Appendix C for an example of how to format the LOI Consensus Review Response.

Revised LOI

CTEP strongly encourages submitting documents with track changes so reviewers can easily see the changes from the last version of the document. When tracked versions are submitted, CTEP still needs a clean copy of the documents for their records. You can either provide a tracked Microsoft Word version and CTEP will accept all of the changes to save a clean version for their records or you can submit both the clean PDF and tracked PDF versions. Submitting only clean documents is permitted but may cause delays as they tend to be more time consuming for CTEP to review. Although it is allowed by CTEP, based on DF/HCC ETCTN experience we do not recommend submitting the same document in two different formats (e.g., submitting the clean LOI form as both a Word document and PDF).

Protocol and Consent Documents

Initial Submission

The initial protocol submission must include:

1. Protocol: The protocol document must be provided as a clean Microsoft Word document that complies with all CTEP eSubmission requirements. Appendix A should be used to ensure the document meets all specifications prior to submission. The submission of PDF documents is optional but based on DF/HCC ETCTN experience we do not recommend submitting the same

document in two different formats (e.g., submitting the protocol as both a Word document and PDF).

2. Consent Document: The NCI Informed Consent Template must be used when developing the model consent form for CTEP studies. Do not use the DF/HCC Informed Consent template and do not insert any DF/HCC specific information (e.g., investigator's name and contact information). When using the NCI consent template, delete text labeled as "Notes to consent form authors" but leave blank lines, "_____" as these will be used by local investigators when preparing their site specific consent form. Appendix A should also be used to ensure the document meets all specifications prior to submission. The submission of PDF documents is optional but based on DF/HCC ETCTN experience we do not recommend submitting the same document in two different formats.

3. Protocol Submission Worksheet (PSW): The PSW is available on the CTEP website. CTEP does not routinely send email announcements when the worksheet has been updated so Protocol Chairs or designated study team members should always download the form directly from the website when preparing a new submission. The PSW can be submitted as a Microsoft Word document or as a text-based PDF.

4. Response to CTEP's LOI Review Comments: If it was not provided earlier, a formal response to the LOI comments must be included as a separate email attachment. Refer to the Responding to CTEP LOI Comments section for details.

5. Study Specific Documents: Carefully review the LOI comments to determine if any supplemental information was requested. Examples of this may include pre-clinical data that was not available during the LOI review or assay information for planned biomarker studies.

Consensus Review with Unofficial Tracked Documents

CTEP will review the protocol and the same table format that was used during the LOI review will be utilized for the CTEP protocol consensus review comments. The comments will serve as the basis for the protocol OEWG conference call so the Protocol Chair should review the comments prior to the call. It is recommended that the Protocol Chair wait until after the conference call takes place before preparing a formal response to CTEP since the comments may change as a result of the conference call discussion. A conference call is only scheduled for the initial protocol review. A call will not be set up by the CTEP PIO for subsequent revisions unless the Protocol Chair requests that one be scheduled.

Microsoft Word versions of the protocol and consent form are required for the initial protocol submission because these will be used to provide the Protocol Chair with tracked edits when the

consensus review is distributed. The comments associated with changes that have been inserted into the protocol and consent will be identified in the consensus review with yellow highlighting. These unofficial documents can be used as the starting point for the first revision. Tracked documents are only prepared by the CTEP PIO for the initial protocol review.

Conference Call Summary

CTEP will provide a Conference Call Summary shortly after the protocol OEWG call. The summary is created by using the original consensus review and adding details regarding the conference call decision for those comments that were discussed. The Protocol Chair and other participants on the call must review the summary within the timeframe specified in CTEP's email (usually 48 hours). The Protocol Chair does not need to provide a formal response (i.e., does not need to fill in the sections labeled "**PI Response**") at this time. He or she is just reviewing the summary to verify the conference call decisions accurately reflect what was discussed on the call. The Protocol Chair or designated study team member can respond to CTEP with comments about the call summary either in the body of an email or by using tracked changes to edit the document directly. If the summary is acceptable, no response to CTEP is required.

Revisions and Amendments

CTEP strongly encourages submitting documents with track changes so reviewers can easily see the changes from the last version of the document. When tracked versions are submitted, CTEP still needs a clean copy of the documents for their records. You can either provide a tracked Microsoft Word version and CTEP will accept all of the changes to save a clean version for their records or you can submit both the clean PDF and tracked PDF versions. Submitting only clean documents is permitted but may cause delays as they tend to be more time consuming for CTEP to review. Although it is allowed by CTEP, based on DF/HCC ETCTN experience we do not recommend submitting the same document in two different formats (e.g., submitting the clean protocol as both a Word document and PDF).

For any revision or amendment that is in response to CTEP comments, the table with CTEP's comments must be copy and pasted at the beginning of the protocol document and the beginning of the consent document. **The conference call summary is considered an amended consensus review and the tables from the call summary should be used as the summary of change when submitting the first protocol revision to CTEP.**

The Protocol Chair must provide a response in bold directly below each comment in the space labeled "**PI Response**". The comments from CTEP fall into one of the following categories:

1) Comments from CTEP or Pharmaceutical Collaborator requiring a Response: For each of these comments the Protocol Chair should make the suitable revisions in the protocol or consent or

they can provide the reason in the "**PI Response**" section of the summary of changes for not making the suggested modifications.

2) Recommendations from CTEP or Pharmaceutical Collaborator: These comments are advisory and Protocol Chair is not obligated to make these changes. The "**PI Response**" section should be used to indicate if the changes were made or declined.

All additional changes made (i.e., those that are not in response to CTEP comments) should be listed in a new table at the end of the summary with the heading "**Additional Protocol Changes by Principal Investigator**".

A hyperlink to the section within the protocol or consent where the change is taking place must be added for each change (both those requested by CTEP and PI-initiated changes).

Refer to Appendix C for additional summary of change guidelines and examples.

Appendix A: Requirements Checklist

General Formatting

- ☐ Protocol and Informed Consent are two separate documents. A copy of the consent is required regardless of whether changes have been made to the document.
- ☐ Print area for paper is 8.5" x 11"
- ☐ Pages properly oriented (when viewing electronically, the reader should not have to rotate any pages).
- ☐ Margins at least ¾ inch (one inch is preferred)
- ☐ Header and footer information not within 3/8 inch from the edge
- ☐ Header and footer need to have the correct document identifiers (study number) and correct version date.
- ☐ Maximum width of tables is 6.5 inches. Details available below.
- ☐ Page numbers must be on all pages with the exception of the title page. Having a page number on the title page is optional.
- ☐ Page numbers must be consecutive and this includes appendices (i.e., do not restart the appendices page numbers with 1)
- ☐ Use Roman Numerals for the page numbers of the Summary of Change at the beginning of the protocol and consent (revisions and amendments only) and use Arabic numerals for the document's main content.
- ☐ MS Word Styles must be used for section heading. Details available below.
- ☐ Protocol documents must have a hyperlinked table of contents. Details available below.
- ☐ Appendices must be included in the table of contents.

Version Date

- ☐ Version date must be included on the protocol and consent document
- ☐ Protocol and consent version dates must be updated for each new submission to CTEP
- ☐ Protocol and consent version dates must be consistent

Hypertext links

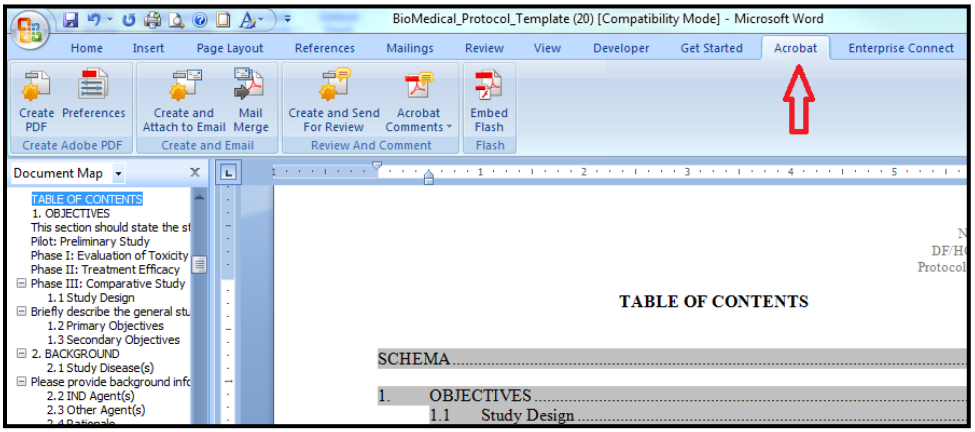
- ☐ Hyperlinks must be used throughout the body of the document to link to related sections, references, appendices, tables or figures that are not located on the same page as the narrative text. CTEP only require linking to the second heading level. For example, if the related section is 5.3.4, the link only needs to point to the heading of section 5.3.
- ☐ A consistent method of designating links should be used (the most common format is underlined, blue font)
- ☐ Relative paths should be used for links. Details available below.

Microsoft Word Documents:

- Cannot be read-only
- Cannot be password-protected
- Cannot contain macros
- Must be saved with a file extension of .doc or docx

PDF Documents:

Note: Microsoft Word documents are always converted to PDFs by the CTEP Protocol and Information Office (PIO) before they are routed to CTEP reviewers and prior to submission to the FDA, when applicable. For this reason, Microsoft Word documents must be formatted in such a way that they are compliant with the PDF submission requirements detailed in this guidance. It is highly recommended that you convert the protocol and consent to PDFs prior to submission to verify they meet the requirements (even if you are only submitting Microsoft Word versions). Adobe Acrobat PDFMaker is an add-in application for Microsoft Word that makes creating CTEP compliant documents easier. If you do not see the Acrobat toolbar in Microsoft Word contact your institution's Help Desk for assistance with installing the add-in.



- Must be text-based (created directly from an electronic source such as a Word document) rather than image-based (scanned paper)
- Bookmarks are required for level 1 and 2 headers within the protocol and level 1 headers within the consent. The section hierarchy must be preserved. Details available below.
- Include a bookmark for the title page, table of contents, and schema. Details available below.
- When the PDF file opens, the initial view must be Bookmarks Panel and Page. Details available below.
- Cannot be password protected or have any security settings

- Cannot be saved as portfolios
- Cannot be saved with attachments, annotations, JavaScript, or dynamic content

Recommendations:

The following are recommendations but it is highly recommended that documents comply.

- Font size between 9-12 pt (12-point font for narrative text; sizes 9-10 are recommended for tables and footnotes)
- Font color is black
- Hyperlinks identified with blue text
- Times New Roman font is preferred. Limit other fonts to the following:

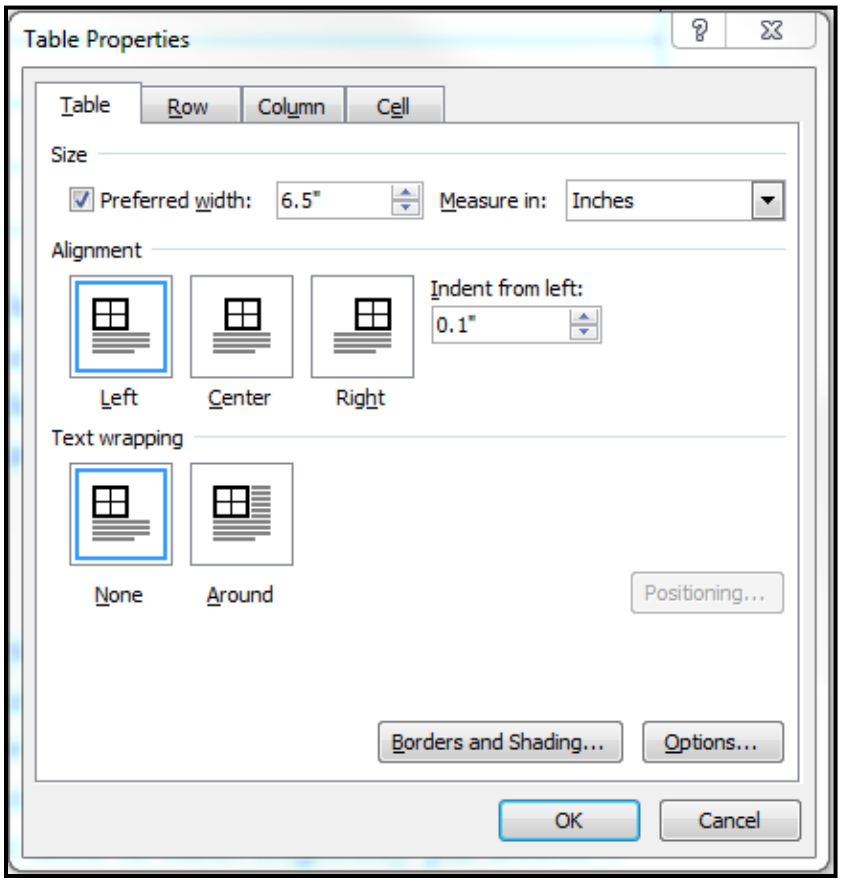
Arial
Arial Italic
Arial Bold
Arial Bold Italic
Courier New
Courier New Italic
Courier New Bold
Courier New Bold Italic
Times New Roman
Times New Roman Italic
Times New Roman Bold
Times New Roman Bold Italic
Symbol
Zapf Dingbats

Appendix B: Formatting Instructions

Table Width

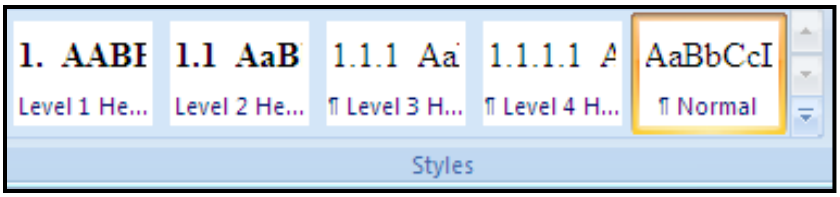
Maximum width of tables should be 6.5 inches

1. Right-click anywhere in the table and select “Table Properties”.
2. Set the “Preferred width” to 6.5 inches



Section Headings

MS Word Styles must be used for section headings. The use of the CTEP protocol template is highly recommended because it has built in styles for heading levels 1-4 and the sections have the appropriate styles already applied.



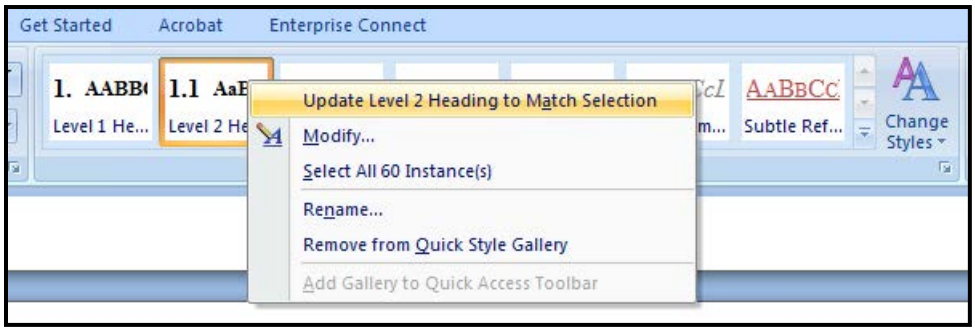
- Protocol: CTEP requires the use of built in styles for at least level 1 and level 2 section headers.
- Consent: The major sections of the consent (e.g., "Why is this study being done?", "What are the study groups", etc.) must also have heading styles applied.

You can use the default style formatting (font type/size/color, indents, etc.) or the formatting can be modified. There are two ways this can be accomplished.

Method 1: Use formatting that is already available in the document.

For example, you change the text for the section 4.2 header from size 10 font to size 12 and then realize you want to make that change to all of the Level 2 Heading text.

a. Highlight the text you want to use as the heading style (i.e., the header text of section 4.2 in the example above)
b. Right-click the appropriate Heading (e.g., Heading 2) in the Quick Style Gallery. Note: If it is not displayed, find it in Styles (Alt+Ctrl+Shift+S).
c. Click "Update Heading 2 to Match Selection".
d. All Heading 2 text will now be size 12.



Method 2: Update the Heading Style formatting directly

a. Right-click the heading style you want to change (e.g., Heading 2) in the Quick Style Gallery. Note: If it is not displayed, find it in Styles (Alt+Ctrl+Shift+S).

b. Click “Modify”.

c. A dialog box with options to change the font, spacing, indent, etc. will be displayed.

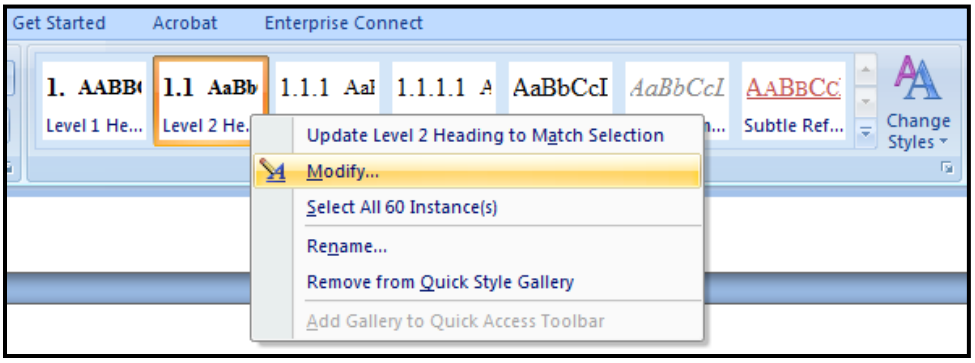


Table of Contents

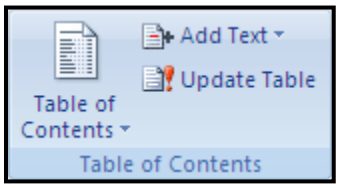
The heading styles will be used to build the Table of Contents (TOC) and convert to Bookmarks in the final PDF document.

Before submitting the document to CTEP, update the TOC and verify that each section header was assigned the appropriate style:

1. Update the Table of Contents.
   DO NOT edit the TOC manually. Follow these steps:

   Microsoft Word 2007-2016

   a. On the **References** tab, in the **Table of Contents** group, click **Update Table**.



   b. Click **Update entire table**.

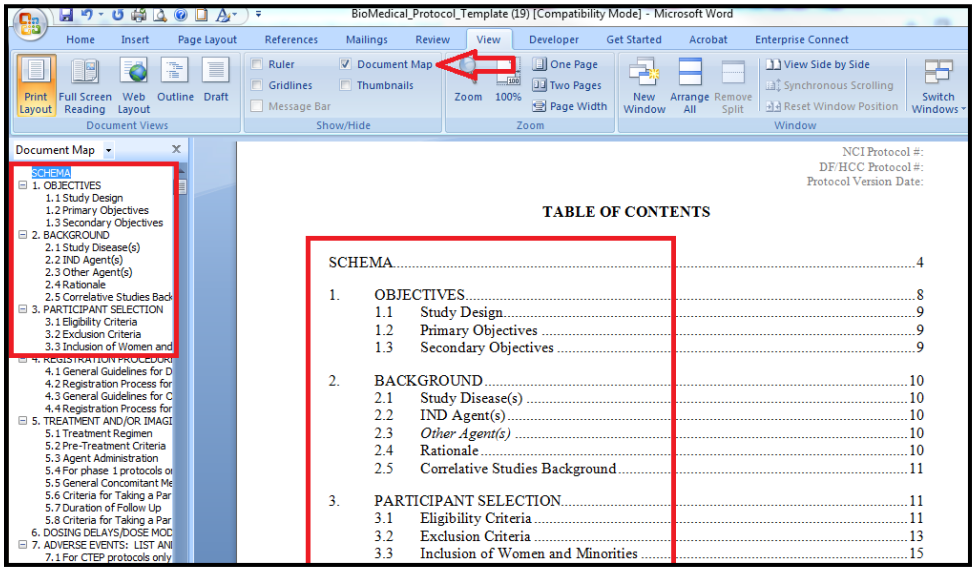
   Microsoft Word 2003

   a. Click the table of contents.

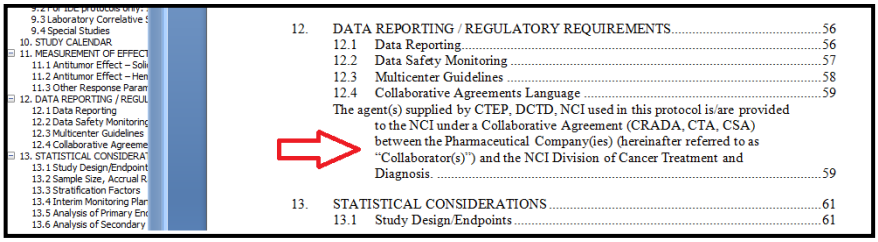
   b. Press F9.

2. Verify that the TOC includes all Level 1 and Level 2 Section Headers. If the Heading Styles were applied correctly to each header, the Document Map or Navigation Panel will match the TOC.

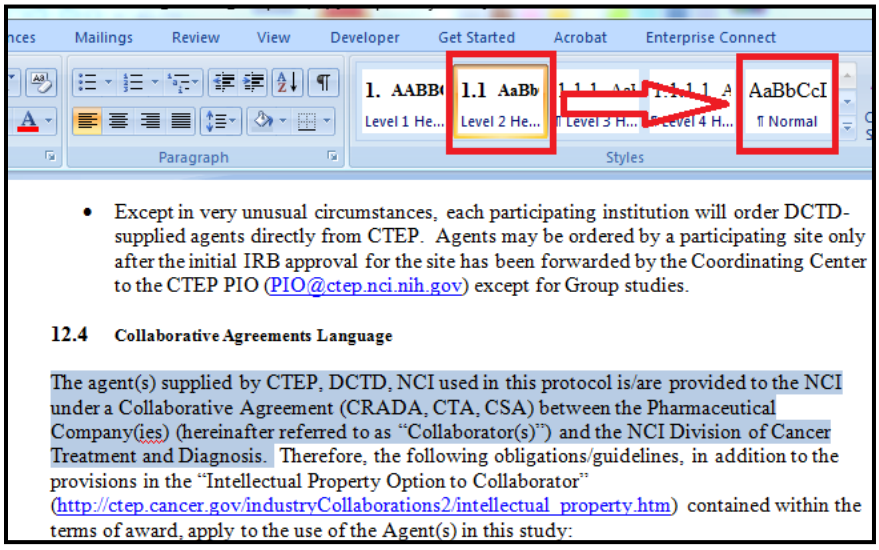
    a. Select Document Map (Word 2007) or Navigation Pane (Word 2010-2016) under the View Tab.
    b. Verify the list on the left-hand side matches the Table of Contents



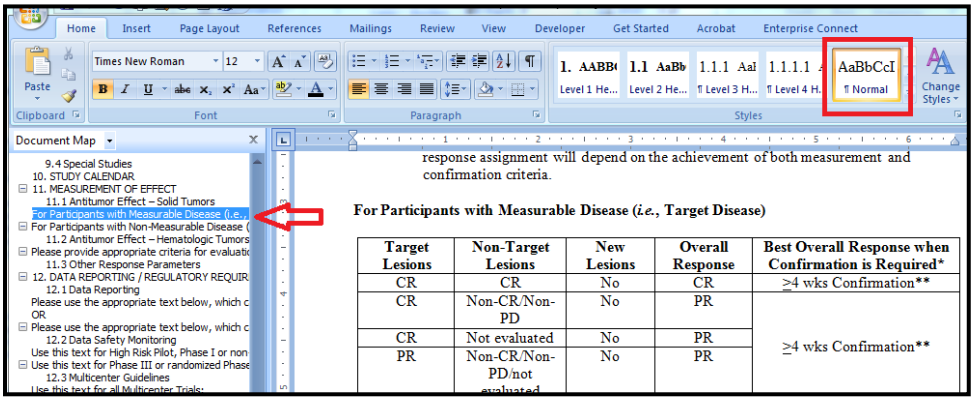
    1) Text that is not a section header may appear in the TOC.



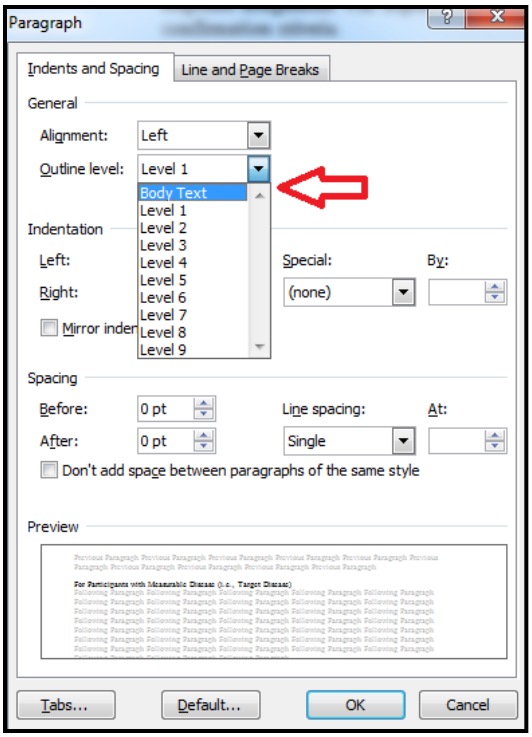
To correct this, navigate to the section of the document that is impacted and change the assigned the style heading style. For this example, the style had to change from Heading 2 to Normal.



2) You may also notice non-heading level 1 or 2 text displaying in the Document Map/Navigation Pane even when the assigned style is "Normal".



To correct this, navigate to the section of the document that is impacted and right-click the text that is displaying in the Document Map/Navigation Pane. Select "Paragraph" and change the Outline level to "Body Text".



Hypertext Links

Always use relative paths when inserting hyperlinks. This will prevent broken links when sections of the document are added, removed, or edited in the future. The easiest way to do this is to link to section headers or established bookmarks.

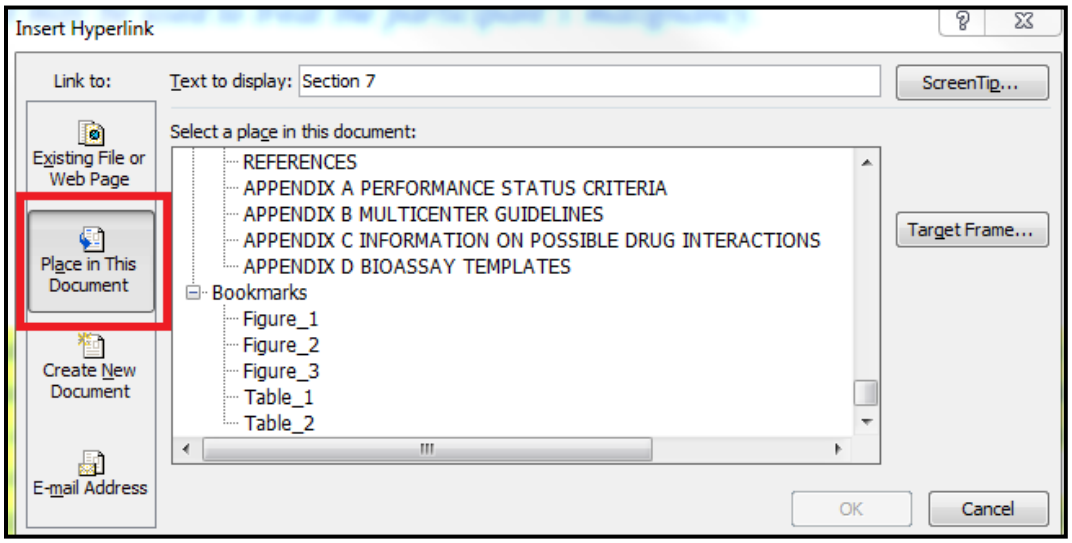
1. Determine the destination of the hyperlink. If it is going to some place other than a level 1 or 2 header, a bookmark will need to be created before the hyperlink is added. Examples of this would be if the link is going to point to a table or figure within the document.

   To create a bookmark:

   a. Highlight the text or item to which you want to assign a bookmark (i.e., the link destination)
   b. On the Insert tab, click "Bookmark".
   c. Name the bookmark (e.g., Figure_3). Bookmark names must begin with a letter and can contain numbers.
   d. Click "Add"

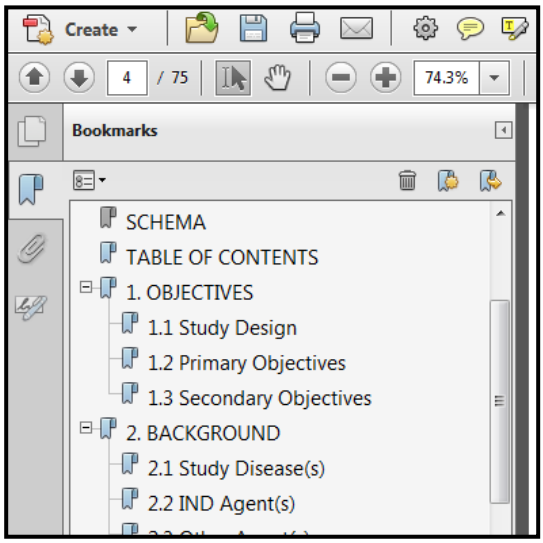
2. Insert the hypertext link:
   a. Highlight the text to which a hyperlink will be added
   b. Right click and select "Hyperlink"

c. Select the option Link to "Place in This Document". Any text that has been assigned Heading Level 1 or Heading Level 2 can be selected. Text that has been assigned as a bookmark is available by scrolling down to the end of the section headers.



PDF Bookmark Hierarchy

When the Microsoft Word document is converted to a PDF, level 1 and level 2 headings must be bookmarks in the protocol and level1 headings must be bookmarks in the consent.

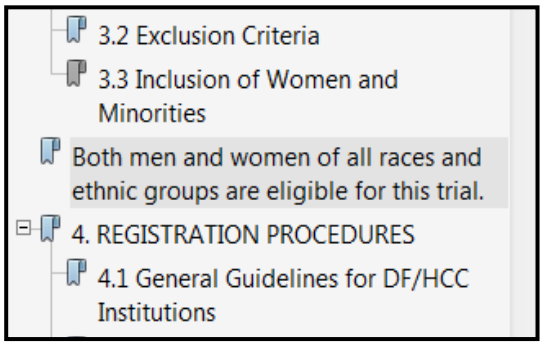


The level 2 headings must display as expandable/collapsible lists under the appropriate level 1 headings (e.g., 1.1 Study Design falls under 1. Objectives).

If they are not displaying correctly, return to the Microsoft Word document and check the assigned Styles. See above for details.

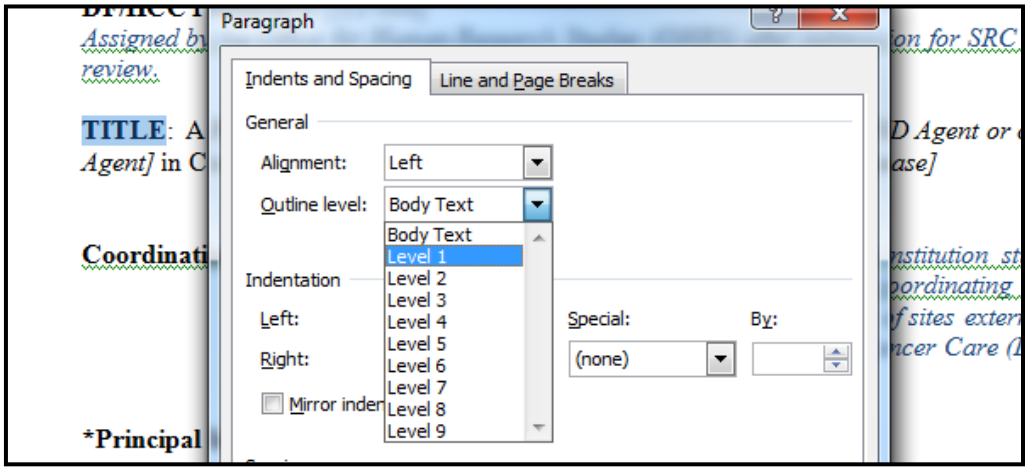
Converting Word Headings to Bookmarks

If non-heading heading level 1 or 2 text is converting to a bookmark in the PDF document, return to the Microsoft Word document and check the assigned Style and Outline level for the text. See above for details.



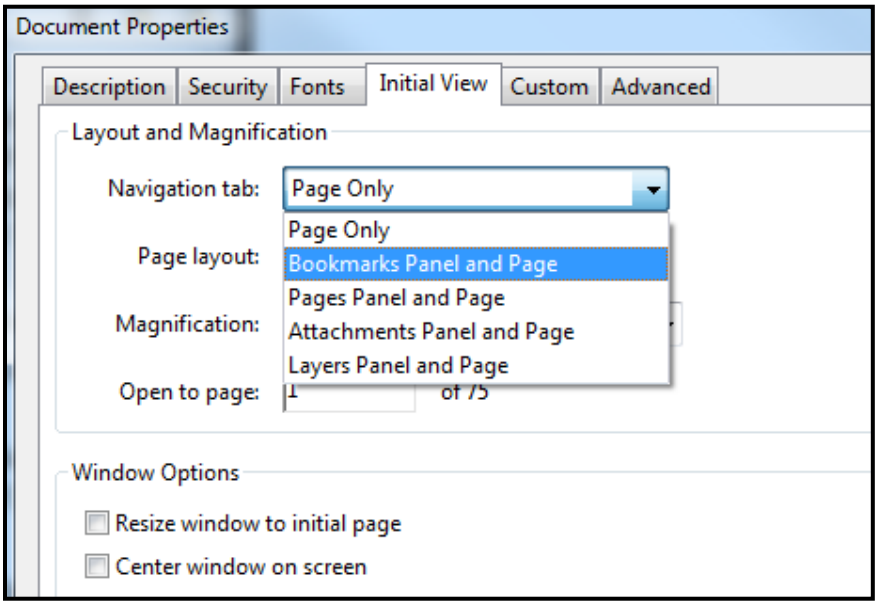
Adding PDF Bookmark for Text that is not a Heading

If you used the CTEP protocol template, the Title page will not automatically convert to a PDF Bookmark. To correct this, right-click the text "Title" on the title page of the Word document. Select "Paragraph" and change the Outline level from "Body Text" to "Level 1". When the Word document is converted to a PDF, the Title should now appear as a bookmark.



Initial View

Within the PDF Document, select “File” and then “Properties”. Under the Initial View tab, verify the Navigation tab is set to “Bookmarks Panel and Page”.



Appendix C: Summary of Change Guidelines and Examples

Example of Response to LOI Comments

Note:

- Hyperlinking the summary of change is not required when addressing **LOI** review comments
- Leave the original comment from CTEP and when applicable, the conference call decision.

✓ **Acceptable:**

#	Section	Comments
1.	n/a	CTEP would like you to consider having the qualified MATCH panel run on all patients at baseline/diagnosis and perhaps at the end of induction. Patients with mutations that would make them eligible for the NCTN MATCH study could be immediately referred to this study, with no delay in treatment at the time of progression if they have an eligible mutation. **OEWG Conference Call Decision**: *The Protocol Chair will consider the logistics of having the panel run on all participants and will provide a response with the initial protocol submission.* **PI Response: The possibility of using the panel for all patients on this study was discussed with representatives from CTEP, the MATCH committee, and the Protocol Chair. It was agreed that this was not feasible as participants on this study will be consenting to a first-line treatment protocol.**
2.	2.5 [or LOI Background Section if a revised LOI was required]	Please provide additional data on genomic scarring. The argument made is that the 3000 SNP analysis can identify good prognosis patients, but the graph on page 5 of the LOI merges high scarring with gBRCAm and does not give the breakdown. **OEWG Conference Call Decision**: *The Protocol Chair summarized the available data on the call. The graph will be revised and additional information incorporated into the protocol document [or LOI document if a revised LOI was required].* **PI Response: We have added additional information regarding the genomic scarring assay to the protocol background (section 2.5) [or page 5-6 of the LOI if a revised LOI was required].**

Examples and Notes when Responding to Protocol and Consent Comments

- Hyperlinking is required when addressing **protocol and consent** review comments
- Leave the original comment from CTEP and when applicable, the conference call decision.
- When responding to the initial protocol consensus review, comments that have been addressed in the unofficial copy of the protocol and consent provided by CTEP will be highlighted in yellow. If the Protocol Chair agrees with the changes, he or she can respond to the comment with "accepted track change". If the change is rejected, the Protocol Chair should indicate this and will need to provide rationale.

✓ **Acceptable:**

#	Section	Comments
3.	3.1.1	Eligibility: CTEP recommends either defining specifically which sources of CLIA-approved BRCA testing will be accepted or using the following language: Due to the long acceptance of BRCA testing through Myriad, Myriad testing will be accepted. If testing for BRCA is done by other organizations, genetic consultation report from a qualified medical professional confirming that the laboratory results showed a recognized germ line deleterious BRCA 1 or BRCA 2 mutation or BRCA rearrangement is required. **Conference Call Decision:** *Investigator agreed with the CTEP provided language for this section.* **PI Response: The provided language has been added.**

⊘ **Not Acceptable** (because the original comment and call decision were removed):

#	Section	Comments
4.	3.1.1	The CTEP provided language regarding CLIA-approved BRCA testing has been added.

✓ **Acceptable:**

#	Section	Comments
5.	Title page	Please change IND numbers to "TBD." CTEP plans to file a combination agent IND. **PI Response: Accepted track change**

Additional Summary of Change Guidelines

- The summary of change should not have any changes that were previously approved by CTEP. When preparing a new revision or amendment, delete the previous summary of change.

- The hyperlinks in the summary of change only need to go to the second heading level within the protocol. For example, if the change is made in section 3.1.1, the link can point to the top of section 3.1. Links to the consent document only need to point to the level 1 section header.

- The same summary of change can be used for the protocol and consent or different summary tables can be prepared.

  For example, if there are six changes being made to the protocol and four changes being made to the consent, you insert a summary of change with all ten changes at the beginning of the protocol and again at the beginning of the consent document. For the protocol, the summary of change would have hyperlinks for the six protocol changes and the summary of change at the beginning of the consent would have the remaining four changes hyperlinked. Alternatively, you can break out the summary of change so only protocol changes are listed at the beginning of the protocol and only consent changes are listed at the beginning of the consent.

- There always needs to be a summary of changes for the protocol even if the only change to the protocol is the version date. If the only change to the consent form is the version date, you do not need a summary of change in front of the consent. In the protocol summary of change, note that the version date update is the only change to the consent. You will still need to submit a copy of the consent document.

✓ **Acceptable:**

#	Section	Comments
6.	Title page	The protocol version date has been updated from 01/02/2016 to 04/05/2016. The consent version date was also updated to 04/05/2016. No other changes were made to the consent form.

- When appropriate, a brief justification for the change(s) should be included in the summary of change. The rationale can be added in paragraph form at the beginning of the document if the majority of changes are being made for the same reason (e.g., a new cohort is added) or the rational can be included in the comment field for the individual change.

✓ **Acceptable:**

#	Section	Comments
7.	3.1.4	The timing for the pregnancy test in the eligibility section was updated so that it is consistent with the study calendar in section 10. Female participants of childbearing potential must have a negative urine or serum pregnancy within 72 hours ~~7 days~~ prior to receiving the first dose of study medication.

- If text is deleted, that should be stated in the summary of change and the hyperlink should point to the section of the document where the text was previously located. If an entire section is deleted, the hyperlink should point to the beginning of the next section.

✓ **Acceptable:**

#	Section	Comments
8.	1.3.1	The first translational science objective has been removed. ~~To examine the expression of PTEN, pAKT, cyclin E, and MET in formalin-fixed, paraffin-embedded tumor.~~

✓ **Acceptable ONLY if you are providing a tracked copy of the protocol:**

#	Section	Comments
9.	1.3.1	The first translational science objective has been removed.

- If there is a straightforward change that is made in numerous locations throughout the document, linking each instance is not always required. If you are unsure if a particular edit will require linking to each instance of the change, contact the CTEP PIO (pio@ctep.nci.nih.gov) for guidance prior to submitting the revision or amendment**.**

✓ **Acceptable:**

#	Section	Comments
10.	*Throughout*	Per the company's request, the drug name has been changed from "X" to "Y" throughout the protocol.

⊘ **Not Acceptable** (because there are likely only a few instances where the change took place and links are missing):

#	Section	Comments
11.	*Throughout*	The maximum accrual number has been updated from 55 to 60.

✓ **Acceptable:**

#	Section	Comments
12.	Schema 1.3 13.2	The maximum accrual number has been updated from 55 to 60.

- The summary of change needs to provide adequate detail about what has changed within the document.

✓ **Acceptable:**

#	Section	Comments
13.	1.3.1	The first translational science objective has been updated. From: To examine the expression of PTEN, pAKT, cyclin E, and MET in formalin-fixed, paraffin-embedded tumor. To: To examine the expression of PTEN, PD-L1, p53, pAKT, and MET in formalin-fixed, paraffin-embedded tumor pre- and post-treatment.

✓ **Acceptable:**

#	Section	Comments
14.	1.3.1	To examine the expression of PTEN, PD-L1, p53, pAKT, ~~cyclin E~~, and MET in formalin-fixed, paraffin-embedded tumor pre- and post-treatment.

✓ **Acceptable ONLY if you are providing a tracked copy of the protocol:**

#	Section	Comments
15.	1.3.1	The biomarkers in the first translational science objective have been updated and the time points for tumor collection added.

⊘ **Not Acceptable** (because the description of the change is too vague):

#	Section	Comments
16.	1.3.1	The first translational science objective has been updated.