EVERYTHING YOU ALWAYS WANTED TO KNOW BUT WERE AFRAID TO ASK: A FOCUS ON STUDY DOCUMENTS

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Rana Leed, MPH

INTRODUCTION

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RANA LEED

- Drexel Dornsife School of Public Health, Health Management and Policy
- Coordinator for MFMU (NICHD network) in Obstetrics – Drexel University in Philadelphia
- Coordinator/Project Manager in Integrative Oncology and Symptom Management – University of Pennsylvania Abramson Cancer Center in Philadelphia
- Regulatory Specialist for CTN (NIDA network) in Substance Abuse and HIV – Oregon Health & Science University in Portland
- Regulatory Specialist for Department of Medicine – University of Minnesota in Minneapolis
- Regulatory Manager for MNCCTN (state funded cooperative group) in Oncology – University of Minnesota Masonic Cancer Center in Minneapolis
- Education Manager – Boston University

EXPECTATIONS AND AGENDA

- Agenda
  - Define essential documents
  - Review general recommendations and best practices
  - Focus on Consents, Eligibility Criteria, Forms and Logs
  - Discuss INSPIR and document management
  - Case Study Discussion - Live demonstration and practice in Word
- Ask questions!
- Out of Scope
  - Not in Scope: Using or operationalization of forms
  - Not in Scope: FDA Part 11 Compliance Requirements

- ✓ Identify the types of essential documents for successful study management and execution
- ✓ Learn best practices for developing and formatting study documents that can be applied to protocols, consents, and various essential documents including forms and logs
- ✓ Demonstrate document management techniques that can lead to successful IRB submissions and study compliance

MANY DIFFERENT TECH OPTIONS

- This will focus primarily on developing documents in Word and REDCap but there are several different software systems can be used
  - Publisher
  - Adobe
  - Excel
  - Others? What have you used to develop forms?
- This will also focus primarily on developing documents for printing out and completing them by hand but forms can also be completed electronically (cloud-based software or on computer)
  - REDCap
  - Excel
  - eRegulatory systems like Advarra or Florence
  - Others? What other systems have you seen?

➢ What we talk about today will, generally speaking, apply to whatever software or system you are using

Your Mileage May Vary

Some of these recommendations are actually personal choice based on aesthetics and own specific ideas about form and function. This presentation is also about how the presenter uses Word and does not imply expertise, would love to see other tips and tricks. Based on your own skill, you may already know most of what I will present on or think that it's too fundamental but let's be respectful of everybody's background and experience.

FOOD FOR THOUGHT

General best practices and recommendations

SAME CONTENT BUT DIFFERENT LANGUAGE

Remember the audience for each document – while copy/paste can save time, might need to edit the language to be appropriate for the audience. Must still maintain consistency as applicable.

INFO APPLIES REGARDLESS OF STUDY

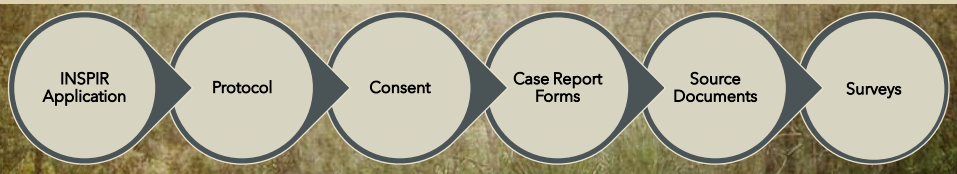
- Industry sponsored study, Multi-Site regardless of Lead or Participating, Investigator-Initiated
- Chart Review, Data + Specimen Collection Only, Survey Study, Observational, Interventional, Randomized Clinical Trial, etc
- All studies require documentation – even if Lead Team or Sponsor providing most of the documents, more than likely local teams still need to build out some forms or logs
- There is no *just doing X* or *only doing Y* – good documentation is always important

ALCOA-C + CEA

- Originally coined by FDA in the mid 1990s
- Has foundation in Good Clinical Manufacturing Practice guidelines
- CEA – Consistent, Enduring, Available

Attributable	• Obvious and clear who collected and entered the information • Obvious and clear who made a change to the information as well as when and why
Legible	• Information, documentation, record should be easy to read
Contemporaneous	• Data or information should be entered as it is observed, collected, learned with signatures and a date
Original	• Document or record should be the original and not a photocopy
Accurate	• All data and information entered is correct with no errors
Complete	• All forms and logs are complete with no missing information and kept up to date

GENERAL RECOMMENDATIONS AND BEST PRACTICES



VERSIONS AND DATES

ALL documents should have versioning → In file name and within document → Numbers, Dates, or Both

Version Numbers

- Recommendation unless template or other scientific reason
  - Do: Version 1, Version 2, Version 3
  - Don't: Version 1.1, Version 1.2, Version 1.3
  - Why? Generally speaking, X.Y-type versioning is ONLY meant to be used when internal/not final drafts are made
    - Example: During initial drafting of protocol with large team

Within Document

- Best practice: in header or footer to ensure on each page
- Might also appear on first page or in version table

Version Dates

- No real "correct" way – but be consistent
- If a sponsor or lead team has a specific requirement – follow what they want
- American" vs "International" standards - just be consistent
  - MM/DD/YYYY vs DD/MM/YYYY

Consistency Issues

- Regardless of where version info appears – be very careful that it is consistent and updated correctly
- Within document: header/footer, version table, first page intro section
- Within document needs to match file name
- Where else does version info appear?
  - Example: If MOP links directly to Protocol or there is an overall Appendix of Study Files

VERSIONS AND DATES

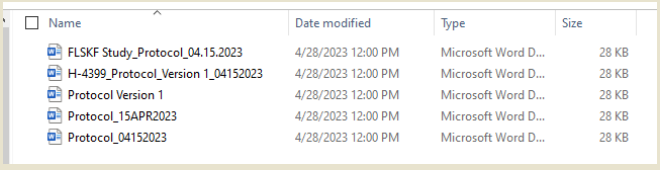
ALL documents should have versioning → In file name and within document → Numbers, Dates, or Both

Examples of File Names and Footers with Version Control

? Which of these do you like the best?

? Why do you like this the best?

? Any other ways this can be done?



Name	Date modified	Type	Size
FLSKF Study_Protocol_04.15.2023	4/28/2023 12:00 PM	Microsoft Word D...	28 KB
H-4399_Protocol_Version 1_04152023	4/28/2023 12:00 PM	Microsoft Word D...	28 KB
Protocol Version 1	4/28/2023 12:00 PM	Microsoft Word D...	28 KB
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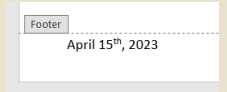
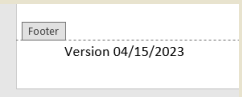
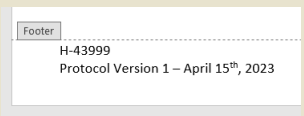






VERSION TABLES

- Mostly used in protocols but could be used in MOPs or SOPs
- Not usually used in consents, forms, logs, etc
- Must remember to update when document is updated
- Sometimes called Amendment Tables
  - Caveat – starting with the first protocol amendment and NOT the first protocol means that version info is not documented for the original

Protocol Version History Table

Version Number	*Version Date*	*Changes*
1	July 15th, 2019	• Not applicable – initial protocol version.
2	April 30th, 2021	• Updated eligibility to clarify that brain metastases is an exclusion • Added hematocrit to Visit 2
3	December 3rd, 2022	• Removed MRI at Visit 10, confirmed that does not impact safety, primary or secondary outcomes

VERBS AND NOUNS – DANGER ABOUNDS

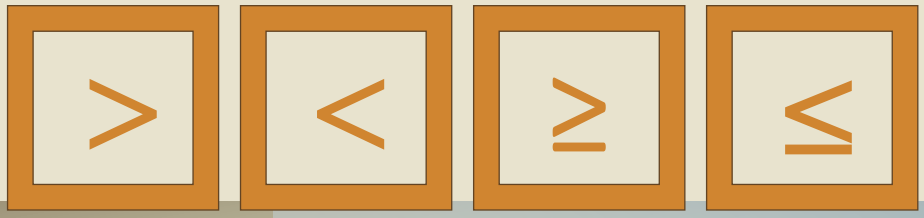
- Don't use "buried verbs" – also called "nominalizations"
  - Definition: expressing a verb or an adjective as a noun
- Don't use a verb where a noun can be used

Don't (or use minimally)	Do
We are doing the research to gain an understanding of how diabetes can have an impact on high blood pressure.	We are doing the research to understand how diabetes impacts high blood pressure.

MINIMIZE USE OF SYMBOLS WHERE POSSIBLE

Greater Than / Less Than / Greater Than Or Equal To / Less Than Or Equal To

- Very easy to insert wrong symbol when developing documents
- Very easy to misinterpret what is meant by the symbol
- Unless space is an issue (like on a table or image) – ALMOST ALWAYS should use the text instead
- Never use symbols in a consent

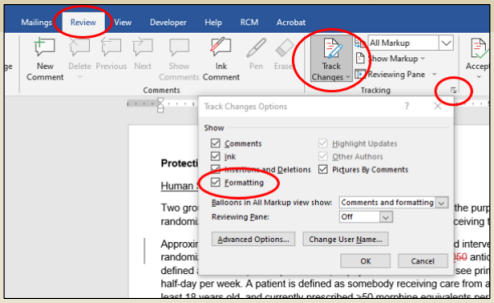


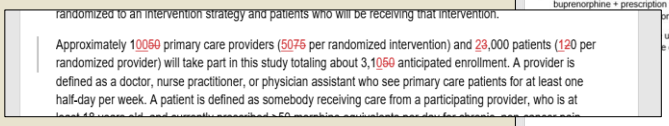
PLAN AHEAD WITH FORMS AND LOGS

- Study management and source documents should all be designed before the study opens for enrollment – even if it's unlikely that they will be used, if them available just in case
  - Adverse Event Form + Log and Deviation Form + Log → Even on data or sample collection or observational studies
- Forms built in Word or REDCap instruments, have them available rather than something happening and not having a good way to document the event
  - Adverse Event and Deviation → Don't scramble to figure out what happened *and* how to document what happened
- While building form, can also come up with the associated process
  - Adverse Event and Deviations → Process for the PI reviewing and assessing, reporting

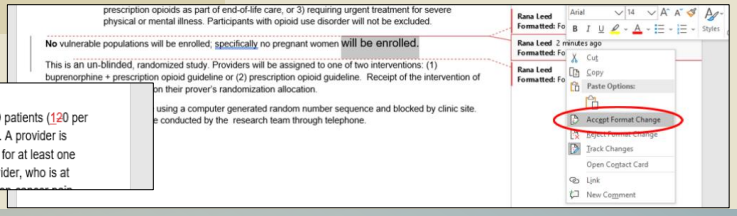
TRACKED CHANGES

- Tracked Change – **a function in Word** to track all changes (text and formatting)
- Lots of documents returned to us "with tracked changes" but not correctly
  - Not manually changing the text to red
  - Not yellow highlighting
  - Not comments
- Accept formatting changes before sending for review or submitting to IRB
  - Font type and size changes, bullet spacing, etc
  - UNLESS IT'S IMPORTANT
  - Don't make people sift through many, many formatting changes to find the actual text or content that was changed




randomized to an intervention strategy and patients who will be receiving that intervention.

Approximately 10060 primary care providers (5075 per randomized intervention) and 23,000 patients (120 per randomized provider) will take part in this study totaling about 3,1060 anticipated enrollment. A provider is defined as a doctor, nurse practitioner, or physician assistant who see primary care patients for at least one half-day per week. A patient is defined as somebody receiving care from a participating provider, who is at


prescription opioids as part of end-of-life care, or 3) requiring urgent treatment for severe physical or mental illness. Participants with opioid use disorder will not be excluded.

No vulnerable populations will be enrolled, specifically no pregnant women will be enrolled.

This is an un-blinded, randomized study. Providers will be assigned to one of two interventions: (1) buprenorphine + prescription opioid guideline or (2) prescription opioid guideline. Receipt of the intervention of on their prover's randomization allocation.

using a computer generated random number sequence and blocked by clinic site.
conducted by the research team through telephone.

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Cut
Copy
Paste Options:
Accept Format Change
Reject Format Change
Track Changes
Open Contact Card
Link
New Comment

HYPERLINKS VS FULL LINKS

- It's almost never useful or appropriate to include the full link of a website
  - *Do not copy/paste* a link directly into a document, slide, email, etc
  - Can create confusion and decrease general readability
  - A major accessibility issue with those who might be using screen readers
- On virtually all systems and computers, hyperlink is available as a mouse right-click.

NEVER	ALWAYS
Complete this form to find out if you are eligible: https://redcap.bumc.bu.edu/redcap_v13.4.13/Surveys/invite_participants.php?pid=10711#:~:text=https%3A//redcap.bumc.bu.edu/surveys/%3Fs%3D98HRK8WpPTRKPE9R	Complete this form to find out if you are eligible.

TEMPLATES

- Don't start from a blank document each time
- IRB templates and CRRO templates
- Study teams can design their own templates that can be used multiple times with some editing for each new study
- Ensures that all the necessary elements are on each form or log
  - Headers, footers, page numbers, study information, versioning

Visit Checklists

Training Logs

Delegation Logs

Informed Consent Note

Adverse Event Form and Log

IRB Reporting Log

FOCUS ON CONSENTS

Are there specific recommendations for consents?

GENERAL CONSENT BEST PRACTICES

- Short sentences – if tempted to use comma or semi-colon – don't! Split into individual sentences for clarity.
- Short paragraphs – if tempted to have a paragraph that is long (4 or more sentences), think about splitting it. Probably there is a good "place" for the splitting.
- Use bullets and tables when appropriate instead of explaining in text – or do both! Just make sure that both text and table match!
  - What happens at each visit
  - If multiple and different reimbursement amounts at different visits

Don't (or use minimally)	Do
The second visit will include a discussion on the risks of the intervention and a review of your medical history. (this sentence also includes TWO "actions", think about splitting into two sentences or a bulleted list)	Visit 2 • Discuss intervention risks • Medical history review At the second visit, we will discuss with you the risks of taking the drug. We will also review your medical history with you.

ELIGIBILITY CRITERIA

How do I write these to be clear and help prevent deviations?

CRITERIA → BEST PRACTICES

Writing Eligibility Criteria

- Age – no symbols, make sure that you aren't excluding lower or upper range by how you are stating it
- Don't need to include "male or female" – unless you are specifically excluding other gender/non-binary
- Don't repeat between inclusion and exclusion
- Be specific – "breast cancer"
  - Are you including DCIS? Are you including Stage 4 or metastatic?

Developing Eligibility Criteria

- Are they for clinical reasons?
- Are they for safety reasons?
- Do they exclude a large part of the population that would, if approved, actually be getting drug or intervention – which means you didn't actually test the drug/intervention on the population
- Don't need to be included in protocol but each of the criteria should have a scientific justification – (clinical, safety, what the patient population looks like, etc)

ELIGIBILITY CRITERIA: TIPS ON HOW TO INCLUDE AGE LIMITS

Confusing, open to interpretation, not as clear	Better → Best
Symbols Exclusion: < 18 and < 70 Inclusion: > 18 and < 70 Exclusion: ≤ 17 and ≥ 71 Inclusion: ≥ 18 and ≤ 70	Less than Greater than Less than or equal to Greater than or equal to
Older than 18 Could mean you can't enroll anybody who is 18	18 years or older
Less than 70 Could mean you can't enroll anybody who is 70.	70 years or younger
Between 18 and 70 Could be interpreted to be only enrolling 19-69 years	18 years old to 70 years old

1. > 18
2. <70

1. Greater than 18
2. Less than 70

1. 18 or older
2. 70 or younger

1. Between 18 and 70

1. 18 years to 70 years old

FORMS AND LOGS

Just what is the difference between a form and log and how do I use them?

FORMS VS LOGS

- Forms *capture information* (more detail, includes signature for review of info)
- Logs *track information* (less detail, provides historical overview of info)
- Some events, procedures, or visits could have both forms and logs → if so, make sure information is the same between form and log!

Adverse Event Form

Adverse Event Log

Visit Checklist

Specimen Collection Form

Specimen Shipping Log

IRB Submission Log

Training Log

INSPIR AND DOCUMENTS

Recommendations on successful applications and submissions

OVERALL RECOMMENDATION

INSPIR Instructions – Start here with questions and learning best practices for INSPIR

How to check status of submission	How to look up training information	How to add new staff to an approved protocol	How to send study correspondence	How to view or print out approval letters	How to find and open a draft initial application
How to respond to a review response	How to revise an existing study document	How to create and submit a continuing review	How to create and submit a final closure report	How to create and submit a RENI	AND SO MUCH MORE

Why does good documentation in INSPIR matter?

- Makes review easier and more efficient
- Faster review and less stipulations
- Poor documentation leads to deviations and continuing noncompliance

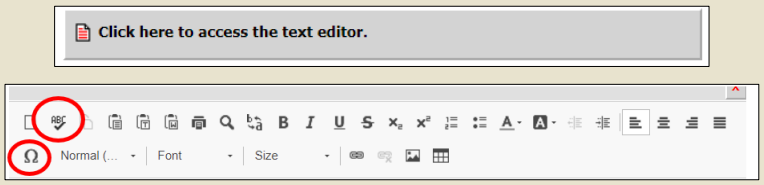
BEST PRACTICES

DO THESE THINGS

- Before submitting, make sure to remove any document that is not going to be submitted or reviewed. Especially important if there are multiple "draft" versions of the same document uploaded.
- Review for spelling errors
  - Red squiggle line or Spell Check in Text Editor

DON'T DO THESE THINGS

- Copy/paste from other documents with symbols in text – often don't copy over correctly



COMMON FILE + NAMING PROBLEMS

- Files that cause trouble in INSPIR
  - Old versions of Office – Word 97
  - Cloud-based system documents – download and then upload
  - Zipped files – unzip and upload individually
  - Formats not same on revised documents
- Industry Sponsored Studies or External Lead Team
  - Protocol Titles, File Names, Version tracking in document sometimes don't match
    - If this is the case – make sure this is explained in document upload space (comments or description)
  - Revised version locked in PDF – attempt to get tracked change version when submitted revised PDF
- Title that is provided in INSPIR is what is put on Outcome Letter
  - Make sure that this title is what needs to appear on Outcome Letter
  - Especially important on studies managed by an external Lead Team or Industry Sponsored studies – may require "proof" that a document has been approved
- Use the same "title" of a document in all places →
  - Protocol Schedule of Events
  - Design/Procedure section of application
  - Document upload pop-up

COMMON DOCUMENT ERRORS

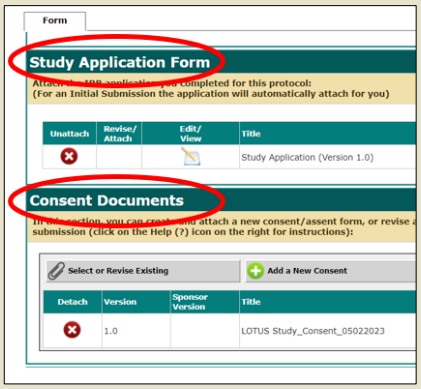
- Documents not attached to study → Only upload or revise a document from within a study
  - Within INSPIR, possible to upload a document without attaching to a study
- Multiple versions of the same document → Prior to submitting – check for duplicates or outdated versions

OUTCOME LETTERS - HOW TO UNDERSTAND THEM

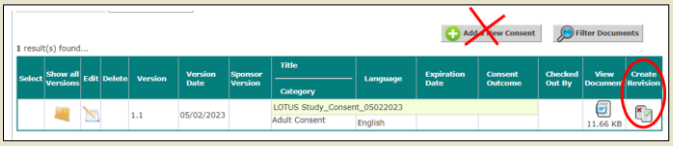
- Not all documents listed – "compromise" all documents with this date approved
- Protocol – version number and version date
  - Amendment, CR, initial
  - Only document specifically called out on outcome letter
  - Version number/date – from document itself mostly
    - Discrepancy between upload popup and document – sometimes will list both
      - DON"T HAVE A DISCREPANCY PEOPLE
- Some very specific nuance to what is called out - uncommon
  - Maybe IIA/IAA
  - Maybe HIPAA
- Special note – will also send in email
- Emphasize reading outcome letter and all associated correspondence with IRB

COMMON MISPLACED OR MISCATEGORIZED DOCUMENTS

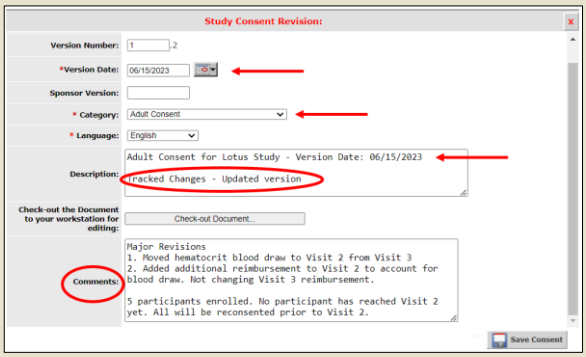
Document	Category	Where	Notes
Protocol	Protocol	Within Application – *In "Separate Protocol"*	If you are uploading a protocol, check off the Yes button when asked.
Consent	Use specific consent type	Initial Submission Packet	This is for all consents – Adult Consent, Parental Permission, Screening Questions Full Consent, Brief Screening Agreement, etc
Exempt Info Sheet	Exempt Info Sheet	Within Application – *In "Study Attachments"*	Do not put this in the Design/Procedures section for attachments. Do not upload in the Consent section.
Recruitment Material	Depends	Within Application – In *Recruitment*	Ensure the category is correct *(flyer vs letter vs recruitment/advertising)*
Questionnaires, Surveys, Interview Guides	Depends	Within Application – *In Design/Procedures "Study Attachments"*	Ensure the category is correct and consistent



REVISING DOCUMENTS – CONSENT EXAMPLE



Reminder – Review and Use INSPIR Instructions How to Revise an Existing Consent Form



LIVE DEMONSTRATION AND PRACTICE

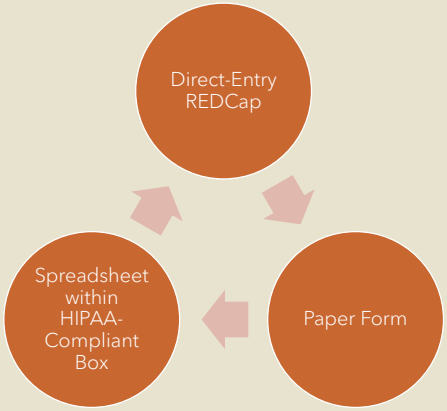
NUMBER ONE RULE

- Use Google – lots of helpful information on how to do various things
- This goes for Word but also is true for REDCap or any other system being used to build forms
- Don't struggle – help exists → email CRRO → we can provide targeted training on specific forms or just chat on a zoom how to do something

REDCAP VS WORD VS ?

Think carefully when developing a form which format or system makes the most sense

Who	•Investigator •Coordinator or Research Assistant •Clinical provider
What	•Data analysis – even if not for outcomes, need to report to somebody on the info or include in a publication? •Primary outcome vs IRB-required reporting vs NIH-required grant reporting vs CONSORT info
When	•During study visit or during clinical visit •Middle of the day or middle of the night
Where	•In coordinator office •In exam room •In community •In hospital room
How	•Asked directly to the participant •Abstracted from medical record •Recorded during study visit



ALIGNMENT TAB

- Use the alignment tab function to set text at both left and right margins when in header or footers
- Rather than using tab or tab-stops which can throw off spacing when things are updated or edited

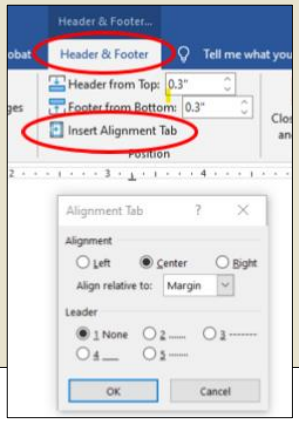


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TABLE FORMATTING TIPS

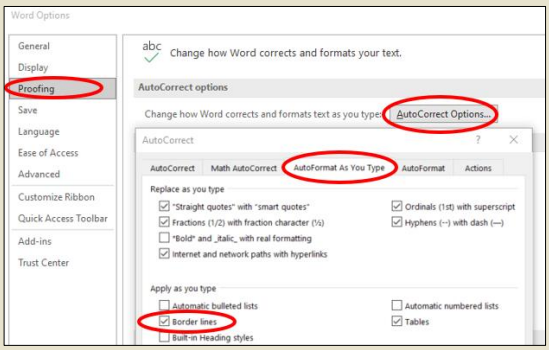
- Auto-Fit to Window for centering – table fits window
- Be deliberate about → depends on how best the info is displayed or documented
  - Horizontal and vertical alignment within cells
  - Merging and splitting cells
- Use bold, left/right margins, other formatting for clarity

Urine Pregnancy Test	☐ Positive ☐ Negative	Date Collected: _____ (mm/dd/yyyy) Signature: _____
Hemoglobin	_____ (g/dL)	Date Collected: _____ (mm/dd/yyyy) Signature: _____
Weight	_____ (pounds)	Date Collected: _____ (mm/dd/yyyy) Signature: _____

Urine Pregnancy Test	☐ Positive ☐ Negative ☐ Not Collected	If not collected, why: _____
Hemoglobin	_____ (g/dL)	If not collected, why: _____ If collected: ☐ In-Range ☐ Out-of-Range Reviewed by, signature: _____ Date Reviewed: _____ (mm/dd/yyyy)
Weight	_____ (pounds)	If not collected, why: _____
All collected on same day – Visit 2 Date Collected: _____ (mm/dd/yyyy) Signature: _____		**Notes:** _____

AUTOFORMAT HORIZONTAL LINES

- Horizontal lines to set apart text in header, footer, or in general text sections
- Border lines must be checked in File → Options
- Use instead of insert line – shapes – line which can have problems with angles



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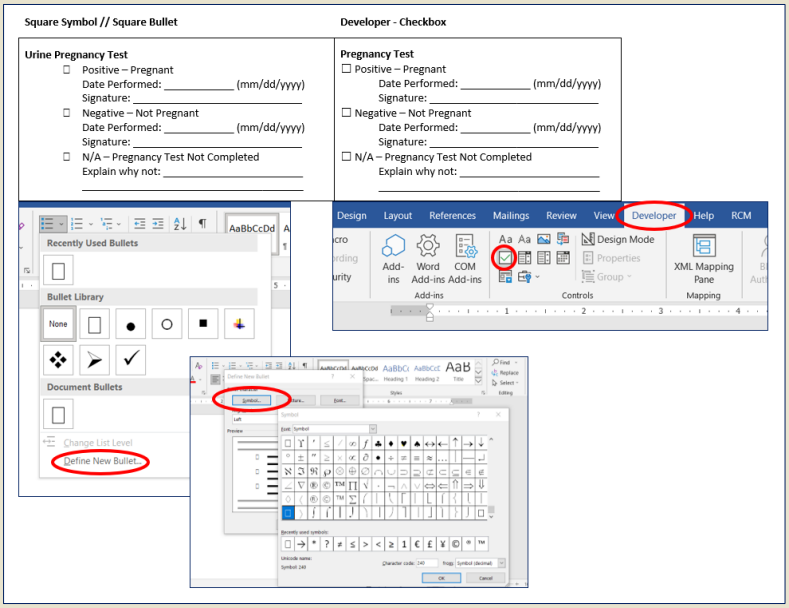
CHECKBOXES VS SQUARES

- Can use Developer in Word to insert aligned checkboxes
- Square symbol does not align properly
- Doesn't really matter but there are options



DEVELOPING TOOLS FROM SCRATCH

Which ones should we practice on?

TOOL OPTIONS

- Adverse Event Log
- Adverse Event Form
- Visit Checklist
- Note to File
- Investigational Product Tracking
- Specimen Collection and Shipping
- Other Options?

USING CRRO TEMPLATES

Which ones should we review?

TOOL OPTIONS

Current tools are undergoing revisions

Self-Assessment Tools have been revised

Other Options?

SUMMARY AND WRAP-UP

OVERALL RECOMMENDATION

Take the time to develop documents, forms, and logs before starting the study

- ✓To collect data in a systematic and consistent way
- ✓To ensure that all visit procedures are completed as required by the protocol
- ✓To provide documentation that those procedures happened as required by the protocol
- ✓To prevent misunderstandings, misinterpretations, confusion with protocol or procedures
- ✓Can impact successful operationalization of protocol

ADDITIONAL RESOURCES

- Clinical Research Seminar
  - April 2023 *Quality Management: Taking a Proactive Approach and Using Self-Assessments to Ensure High Quality Research*
  - November 2022 *REDCap: Case Studies*
  - September 2022 *REDCap Basics*
  - November 2021 *Case Report Form Design*
- RPN Workshop
  - January 2023 *The What, Why, and How of Study Document Management*
  - April 2022 *REDCap Advanced Features*
  - March 2022 *Basics on REDCap: A Tool for Data Collection and Management in Clinical Research*
  - November 2022 *Basics of Developing Source Data Collection Tools and Case Report Forms for Clinical Research Studies*
- Slides and Recordings will be made available after today
- CRRO is always available to review more in-depth any of what was discussed today or how to apply the learning to your specific study