Safety Extrapolation in Pediatric SLE: Opportunities and Challenges

FDA-CERSI Pediatric SLE Workshop

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Challenge: Tensions between Wanting More Safety Data AND Faster Pediatric Patient Access to New Therapies in SLE

Negotiate plans with agencies; generate RCT data → **Off-label prescribing (or lack of access) while awaiting pediatric data** → **A "stronger label", less uncertainty**

- **RCTs are generally unappealing due to risks associated with placebo**
- **Diminishing equipoise over time**
- **Small pediatric datasets- must leverage the much larger adult dataset**
- **Pre-pediatric approval safety information- access is variable, dosing inconsistent**

Can and Should Extrapolation of Safety Streamline Development in Pediatric SLE?

- Old Mantra was “Safety Cannot be Extrapolated”- 2023 ICHE11A Guidance Changes this Approach

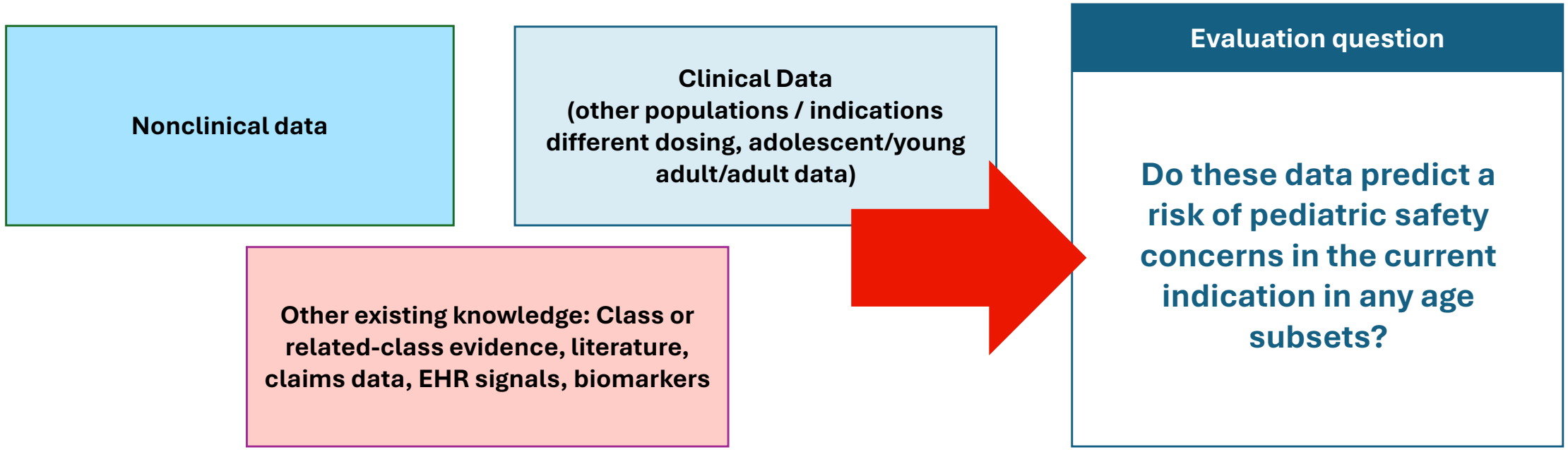
Develop Extrapolation Concept- integrate all available evidence- PK/PD, dosing, safety.
Evaluate strength of evidence, uncertainties, knowledge gaps.

Creation of Extrapolation Plan (define objectives of your studies- PK/PD, safety, efficacy).
Outline methodologic approaches to address uncertainties and knowledge gaps.

Generate data according to the plan, submit the data in support of a product benefit-risk assessment in pediatrics.

ICH E11a (2023): Present the evidence portfolio to support extrapolation of safety (separate from efficacy) at comparable exposures as adults

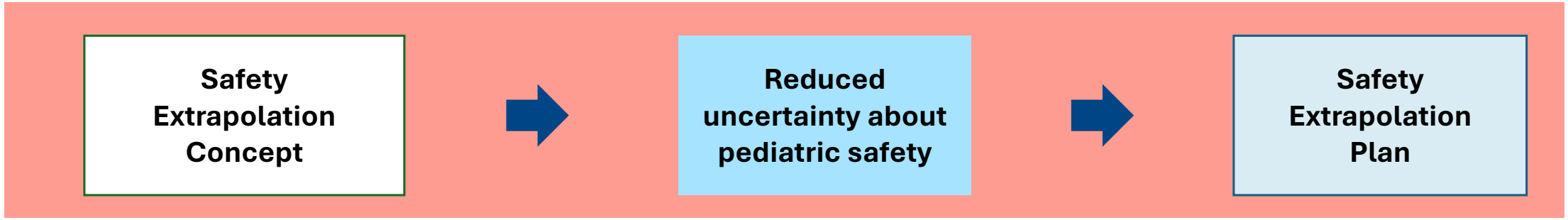
Evidence portfolio to support safety extrapolation



Decision point: where the evidence portfolio points to low residual pediatric divergent safety risk from the adult population, safety should be extrapolated

J&J

When there is a low likelihood of pediatric-divergent safety concerns, development should be streamlined with an extrapolation plan



Up-front, transparent evidence package demonstrating likelihood of pediatric-divergent safety

Tailored safety generation (eg open-label safety study, data supporting formulation/device, post-approval PV signal monitoring)

Outcome: earlier responsible pediatric labeling with a plan to monitor safety as real-world experience accrues.

Where there is a higher risk of pediatric-divergent safety concerns, Sponsor assesses the benefit-risk of the product in pediatric subsets

Evidence suggests pediatric-divergent safety concern → **Benefit-risk Assessment in the Indication** → **Choose a pediatric development path based on severity, reversibility, and expected benefit**

Option 1: No development- PSP/PIP waiver based on safety concerns

When the safety concern makes benefit-risk unfavorable for defined pediatric subpopulation(s).

OR

Option 2: Design study to answer safety questions

Design targeted evidence generation around the specific risk question.

Potentially randomization, risk mitigation, staged enrollment, and longer-term data generation

Decision point: when pediatric-divergent safety is a greater risk, move from streamlining to a proportional benefit-risk plan—waive studies where risk outweighs benefit, or design studies where uncertainty can be resolved.

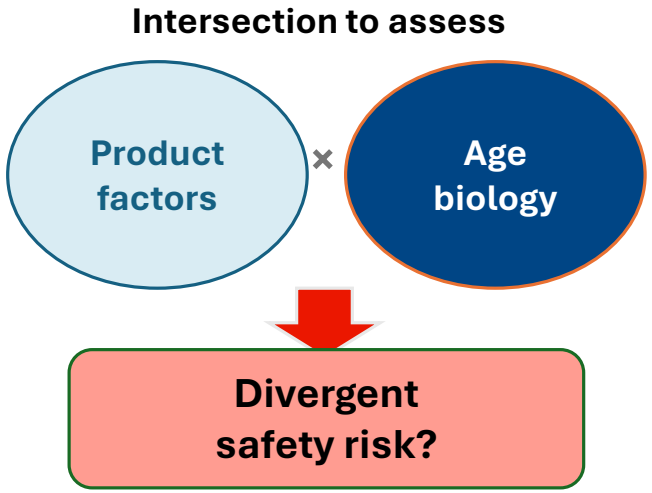
J&J

Age-specific biology may change risk for divergent safety concerns

Infants

1. **Growth + development**
   Many systems (eg GI, skin, immune, brain) still maturing
2. **Body surface area**
   physiology can shift exposure
3. **Formulation / presentation**
   Typically differs from adult considerations

Higher differential-risk plausibility



Adolescents

1. **Puberty + growth**
   active transition may or may not matter
2. **Neurocognitive development**
   developmental vulnerability
3. **Body weight / exposure**
   often closer to adult range
4. **Adult-like formulation/presentation**
   may overlap with adults

More overlap with adult context

Implication: tailor the evidence plan to where developmental biology creates likely pediatric-divergent risk

J&J

Extrapolation Concept for Safety- small vs. large molecule makes a difference when considering potential for pediatric divergent safety

Large Molecule (monoclonal antibody)	Broadly similar ADME characteristics, not metabolized through CYP enzymes, undergoes proteologic degradation		Clearance largely influenced by body size/weight, inflammation burden, serum albumin, immunogenicity (neutralizing anti-drug antibodies)
Small molecule	Conventional PK		In infants, developmental changes affect CYP enzyme activity

****Differences in concomitant medications used in children should be considered**

The Extrapolation Concept for Safety:
Are there on or off target effects that are relevant to pediatrics?

- Panels assessing secondary pharmacology and off-target binding, consider whether these targets play a role in developmental biology (eg growth and development, puberty, neurocognition)
- Range of downstream on-target effects, considering developmental biology

If there is low likelihood of divergent pediatric on or off target effects, extrapolation of safety may streamline development.

Burckart et al. Pediatric Developmental Safety and the ICH E11A Extrapolation of Safety. Br J Pharmacol 2025

The Extrapolation Concept for Safety:

Does the modeled dose lead to exposure comparable to a range that was safe and effective in adults, and does this exposure range predict specific toxicity in the target pediatric subsets?

- PK modeling and simulation approaches to dose selection should be used and transparently explained
- Confirmation of expected exposures in pediatric studies may be an important component of the plan.
- Quantitative Systems Pharmacology modeling can indicate expected toxicity (or lack thereof) in the extrapolation concept.
- **SLE doesn't affect toddler/infant ages, where there is increased pediatric divergent risk**

Burckart et al. Pediatric Developmental Safety and the ICH E11A Extrapolation of Safety. Br J Pharmacol 2025

Some High-Level General Industry Perspectives

Program Risks

Adult Phase 2 may not succeed.
Early pediatric investment can be stranded if the adult program fails.

Evidence Burden

RCT's enroll slowly, particularly with PBO or active comparator that they failed already.

Safety registries are often not scientifically robust and difficult to operationalize and interpret.

Can efficient, targeted pediatric safety evidence generation under extrapolation reach a common goal to bring medicines to children with SLE?

Focus on Quality and Efficiency

The Patient is Waiting

Avoid generating data that isn't necessary or scientifically robust.

Answer the questions that need to be answered.

Key Challenge: Alignment across agencies
Agreement on Concept and Plan for Safety Extrapolation

Very hypothetical examples:

- A randomized study with sham injections to maintain dose blinding is required by EU, but not US
- A 10- year safety registry is required by US, but not EU

Misalignment and associated delays raise concerns across industry, KOLs, investigators, regarding the value/importance of pediatric studies.

Summary- Extrapolation of Safety in Pediatric SLE

When low risk of divergent pediatric safety, **extrapolation must streamline development** (according to ICHE11A)

- **We should only generate the data that are needed pre-approval to reduce burden on patients and inefficiency.**
- Generate a transparent Safety Extrapolation Concept that incorporates pre-clinical, clinical, and other knowledge, to support the proposed study design (for example: open-label PK/PD)

When there is risk of a divergent safety concern in one or more age subset, a different approach is needed.

- Waiver; OR design studies to address safety concern in that age subset

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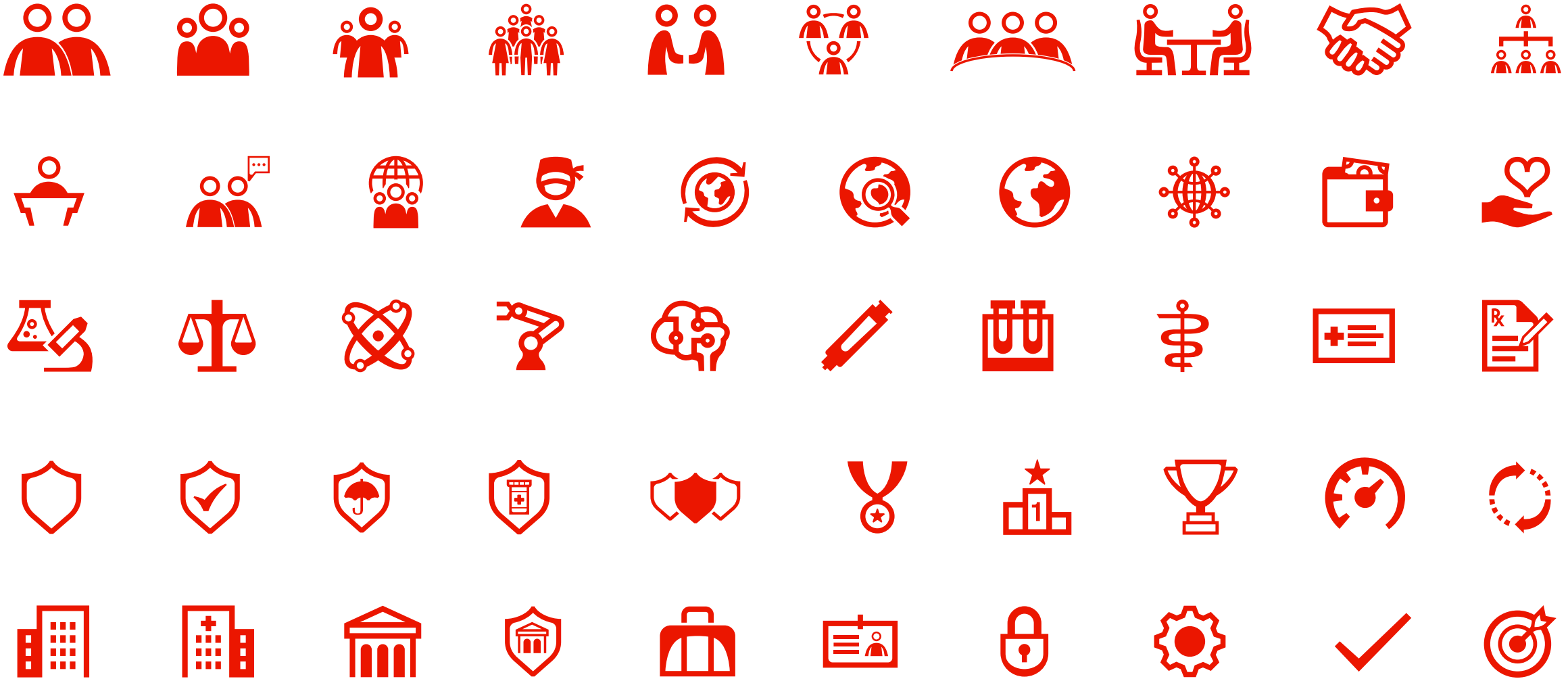
A method for Cross-Agency alignment on the Extrapolation Concept and Plan (efficacy and safety) would expedite development in pediatric SLE.

The extrapolation concept/plan for an active lupus nephritis indication may require special considerations.

Frequently used icons

For additional icons, see our complete icon library



Thank you

If you have more questions, please contact:
Firstname Lastname
firstname.lastname@jnj.com
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Frequently asked questions

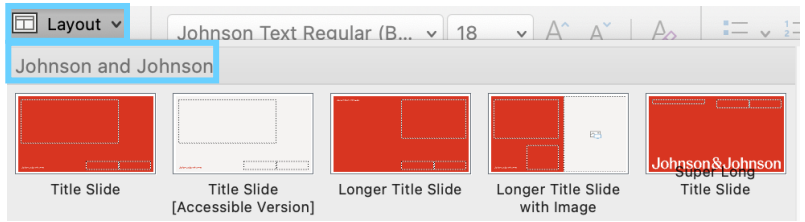
1. Font troubleshooting
    a. Removing embedded non-Johnson Text / Display fonts
    b. Fonts aren't displaying accurately, or the bold button isn’t working correctly
2. Copy and pasting slides
    a. Removing master slides that are from other templates
3. Reducing file size
4. Exporting as a PDF
5. Using the theme colors
6. Resolving blurry imagery

1. Font troubleshooting

Ensuring all slides are using the right template/layouts

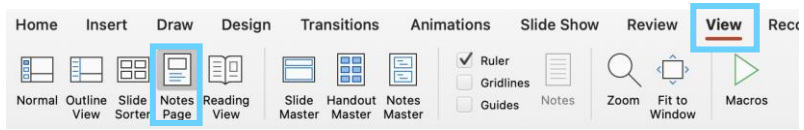
Use these steps to manually check and resolve issues you may experience with fonts.

1. Check and change all slides to use only Master layouts.
2. Manually check all slides.
   - Use the Clear All Formatting tool to reset type.
   - Note: This will remove any bespoke formatting.
4. Check and change all Notes.
   - Use the Clear All Formatting tool to reset type.
5. Check fonts used in charts and tables.
6. Ensure all bullets are using the bullet / numbering button.



1. Changing slides to master layouts in the Johnson & Johnson Template.

2. Clear formatting tool.



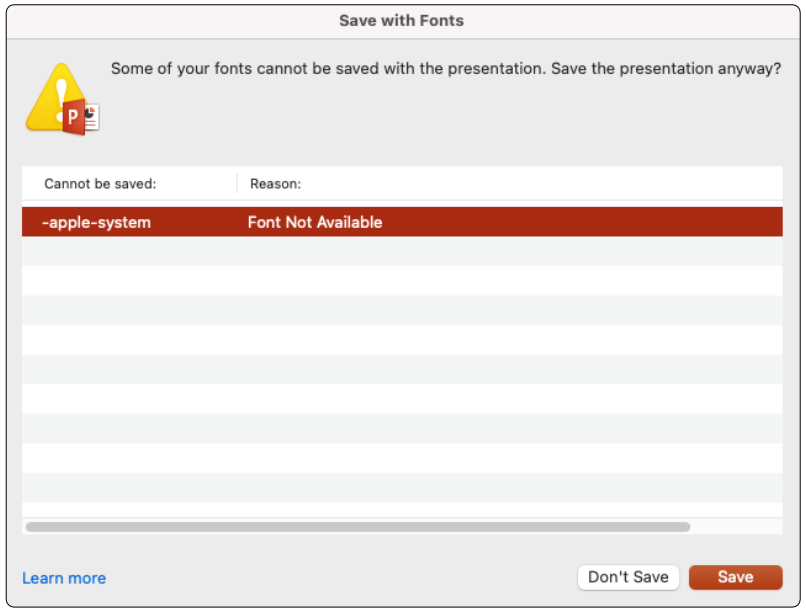
3. Checking Notes.

1. Font troubleshooting

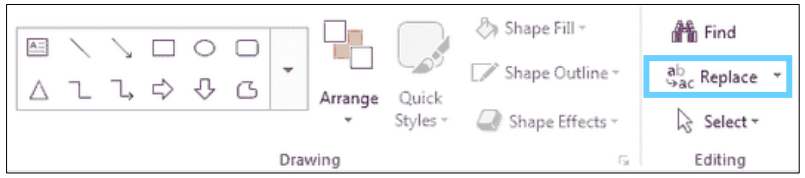
Removing non-brand fonts

Use these steps to manually check and resolve issues you may experience with fonts.

1. When copying previous slides or text from external sources into presentations it may bring in other fonts. This will cause an error message when attempting to save.
2. Use Replace Fonts tool to remove these other fonts.
   - Select the font that needs to be replaced, e.g. Calibri
   - Select Johnson Text Regular to replace the font
   - If Johnson Text Regular is not available, use Arial.



1. Error message when saving file.



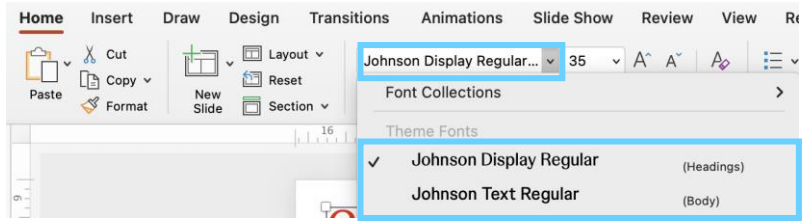
1. Replace Fonts tool.

Font troubleshooting

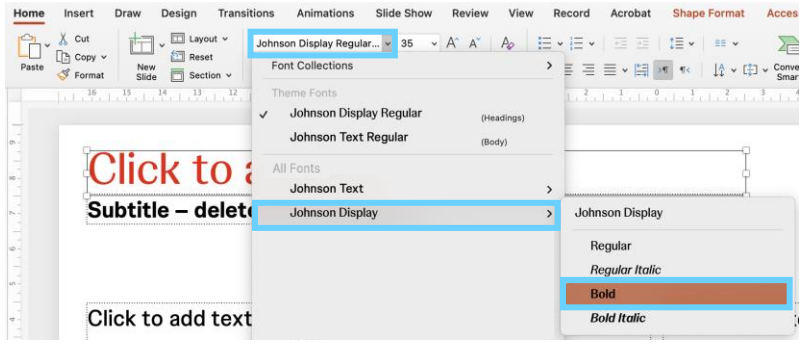
Fonts aren't displaying accurately, or the bold button isn’t working correctly

Use these steps to manually check and resolve issues you may experience with fonts.

1. If the font isn’t displaying correctly, reselect from the Theme Fonts drop down.
2. If selecting Theme Fonts doesn’t resolve the issue, manually select the desired weight from the drop down (e.g., Bold).



1. Select Theme Fonts.



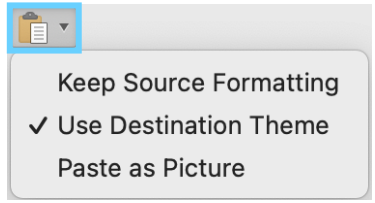
2. Manually select font weight.

Copy and pasting slides

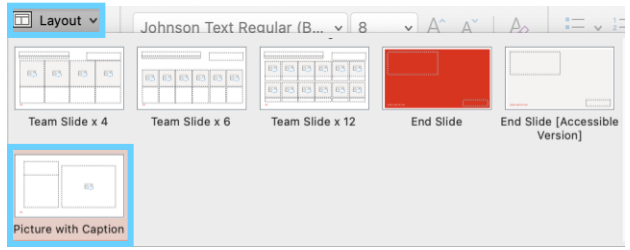
Removing master slides that are from other templates

Use these steps when you copy over sides from other presentations to limit errors.

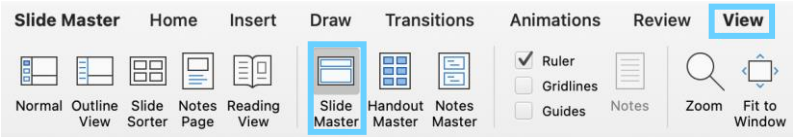
1. When copying over slides select Use Destination Theme in the clipboard icon drop down. This icon appears a couple of seconds after pasting the slides.
2. Copying slides over may result in extra layouts being added to the master template. These layouts need to be changed to another layout.
   - Top tip to spot this: It appears after the End Slide layout.
3. If possible, go into the Master to find and delete the rogue extra layout.
   - This is not essential but may cause font issues.



1. Select Use Destination Theme.



2. Example of a rogue extra layout being added to the Master.

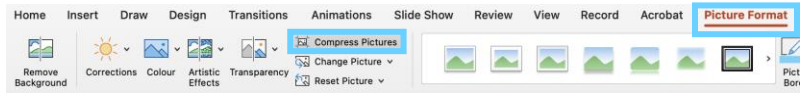


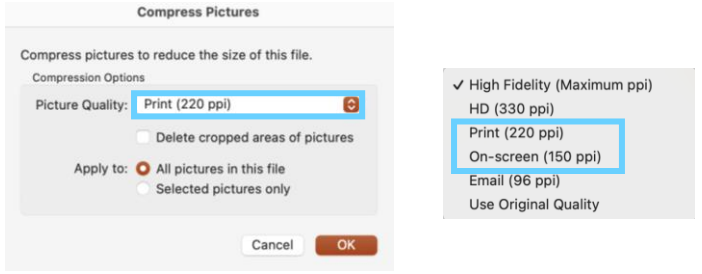
2. Select View and Slide Master to access, locate and delete the rogue extra layout.

Reducing file size

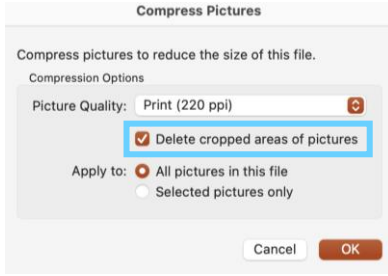
Use these steps to help compress large presentations (to be sharable) and to prevent slowing machines down.

1. Remove unused slides, pictures and videos.
2. Compress inserted images.
   - Select either Print (200 PPI) or Onscreen (150 PPI).
3. Discard editing data for images.
4. Avoid creating image effects with PowerPoint.
5. Check the Master Slide for rogue extra layouts (see previous slide).
6. Send as PDF. This automatically compresses file size.





1. Compress inserted images.

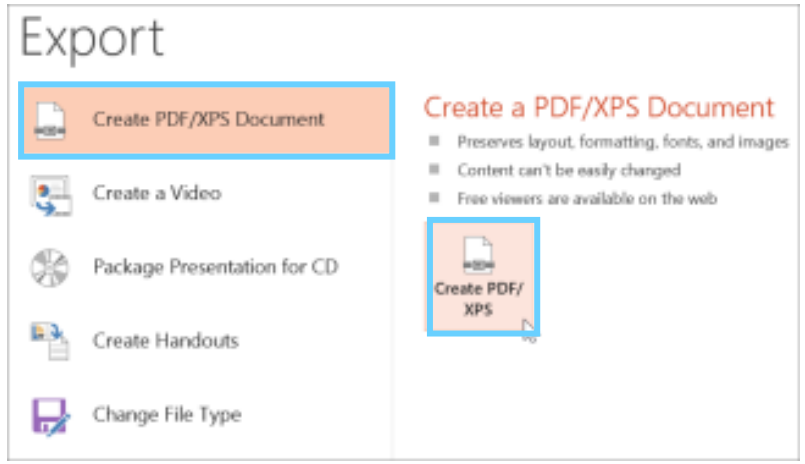


2. Discard editing data for images.

Exporting as a PDF

When you save a presentation as a PDF file, it freezes the formatting and layout. People can view the slides even if they don't have PowerPoint, but they can't make changes to it.

1. Select File and then Export.
   - Click Create PDF/XPS Document; then click Create PDF/XPS.
   - In the Publish as PDF or XPS dialog box, choose a location to save the file to (if you want it to have a different name, enter it in the File name box).
   - Click Publish.

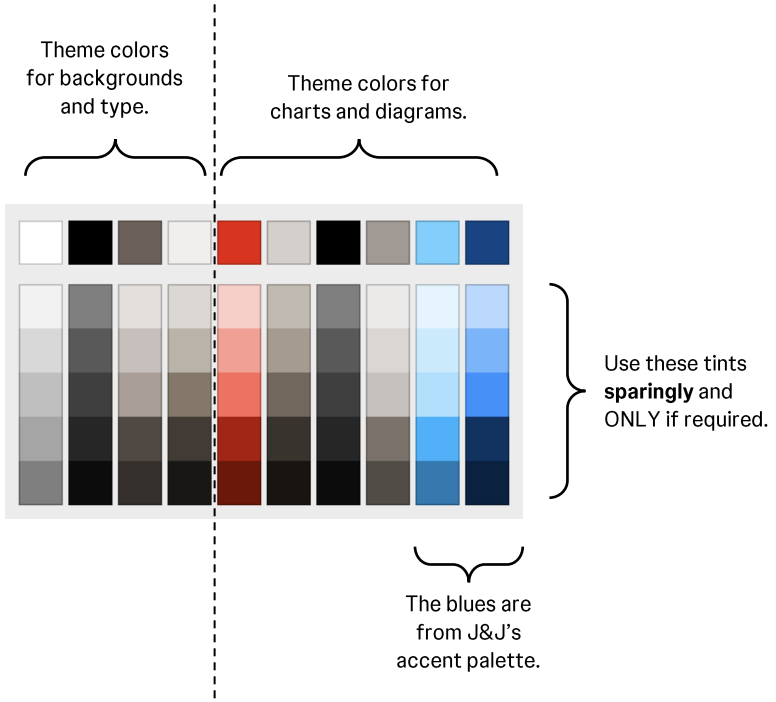


1. Saving as a PDF.

Using the theme colors

See slide 29 in this document for further guidance on accessibility.

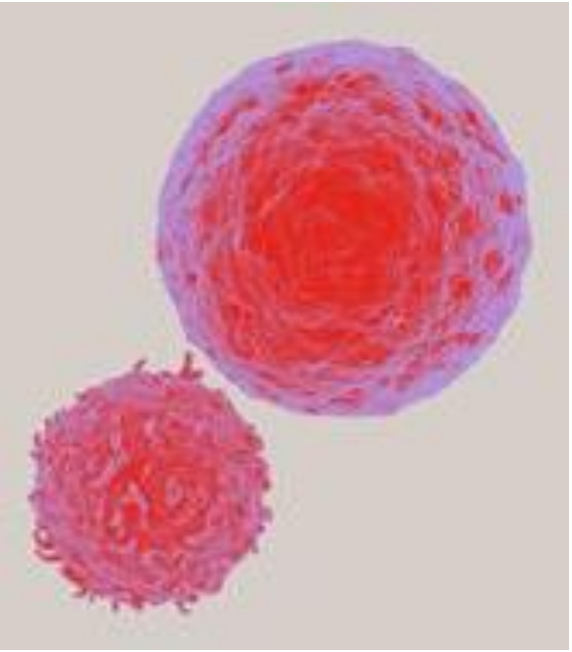
1. Use the preset theme colors in order:
   - J&J Red, light gray, black, medium gray, light blue, dark blue.
   - They can be found in the Shape Fill / Outline drop down.
   - **The blues should ONLY be used for data visualization.**
2. The theme colors have been extensively tested to ensure they are compliant for color blindness accessibility.
   - Note: If the color order is altered, it will affect the visibility and may not be compliant.
   - The tints can not guarantee accessibility.
3. If you require more colors, please see the brand guidelines.



Using imagery

1. When imagery is blurred (see opposite for example) it will need to be reinserted at a higher quality. The recommended settings are:
   - Height (full slide): 1080 pixels
   - Width (full slide): 1920 pixels
   - Resolution: 144 DPI minimum – 220 DPI recommendation
   - If your image is not full height or full width the dimensions may differ from the above.
   - Smaller image sizes can be used to reduce file size
2. If the images match the dimensions above but continues to be blurry, contact IT support to check all software is up to date.

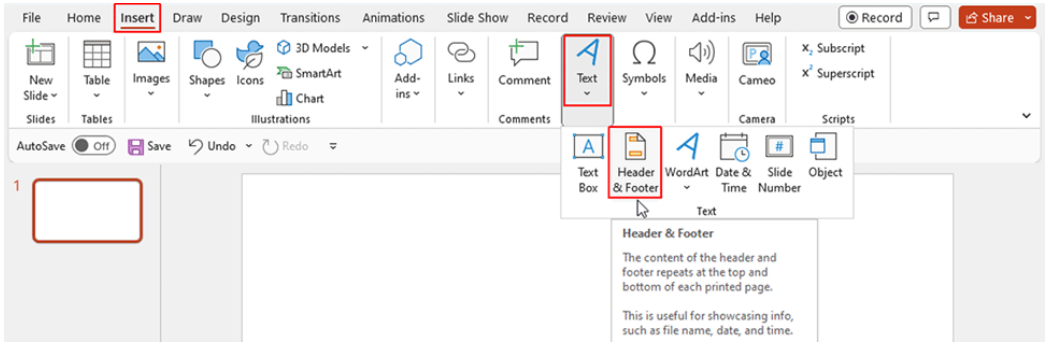
Blurry icon example



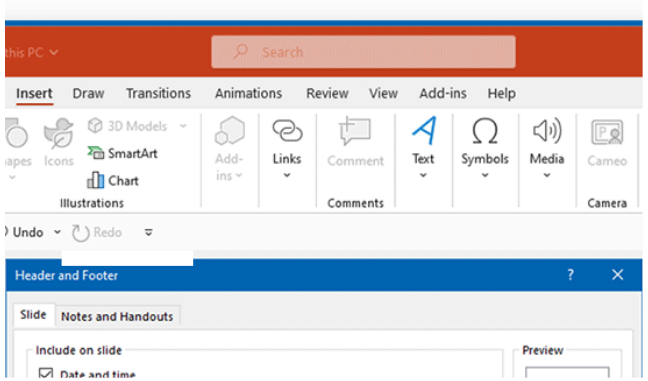
Blurry picture example

How to edit the slide disclaimer and footer

1. If you want to edit the slide disclaimer and footer:
   - Click Insert
   - Click Text
   - Click Header and Footer
2. Toggle tick boxes to turn on or off and enter in the desired footer text with slide legal disclaimer
   - It can also be hidden from the title slide by selecting the Don't Show on the title slide
   - Select Apply to apply the change to the current slide or select Apply to All to apply the changes to all slides.



1. Where to find the Header & Footer function



2. Toggle tick boxes to turn on or off and enter in the desired footer text with slide legal disclaimer