iRIS Office Hours

Phase I Focus

Tuesday, May 25, 2021

Topics

- Changes to Order Set Build Process (Phase I and I/II)
- Dose Cohort vs Amendment
  - Using the Dose Cohort form for phase changes / transitions to expansion
- Strategies for multiple amendments
- General Q&A

Order Sets Process Change

These changes will be only applicable to Phase I and Phase I/II protocols, regardless of which phase we are joining.

Changes to Pharmacy Order Sets

- Current Process
  - All cohorts and dose levels are built in OnCore.
  - All pre-defined dose levels and cohorts are built and validated prior to approval of the NPA / AM, even if they aren't being opened immediately.

- New process for **phase I and phase I/II protocols only**
  - All cohorts and dose levels will still be built in OnCore.
  - Only a single "shell" dose level will be built and validated. This may or may not match what first opens at activation.
    - Pharmacy will be requesting information from study teams on the phase of the study (e.g., if we know we'll only be joining at a later phase)
  - Additional dose levels and cohorts will be built as needed based on Amendments and Dose/Cohort submissions that request a dose level be built and opened.

How does this impact New Protocols?

Initial submission is submitted

SRC, Pharmacy Feasibility, and Nursing Feasibility are complete

Order Set Build

- All cohorts and dose levels created in OnCore
- Only one dose level is built and validated in institutional order set system

Activation

- No dose levels are requested on the ORC.
- Protocol opens to accrual to allow consent and screening to begin.
- **No dose levels will be opened with the initial submission.**

For Phase I and I/II trials only:

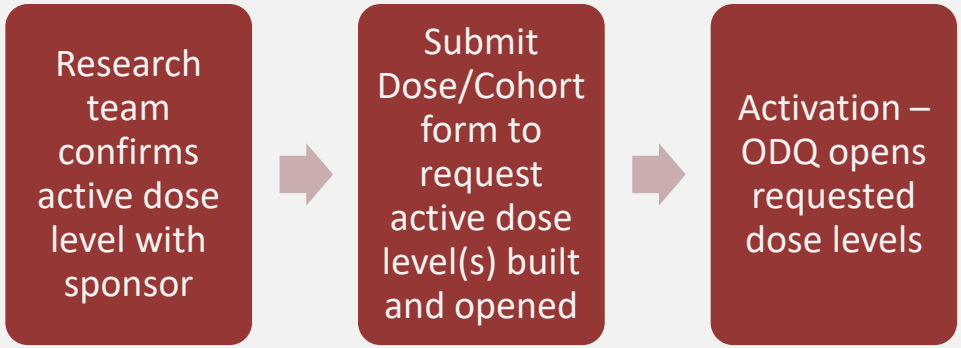
- Research teams will see all cohorts and dose levels built in OnCore
- Not all will be built and available in your institution's order set system
- All cohorts and dose levels will remain suspended when the initial submission is activated

Additional Step to Open Dose Levels

If the NP is activated to a status of **open to accrual**:

Research teams will need to **submit a separate Dose/Cohort form** once the active dose levels confirmed.

Subjects can be consented and screened but **cannot be fully enrolled and begin treatment** until at least one arm is open in OnCore.



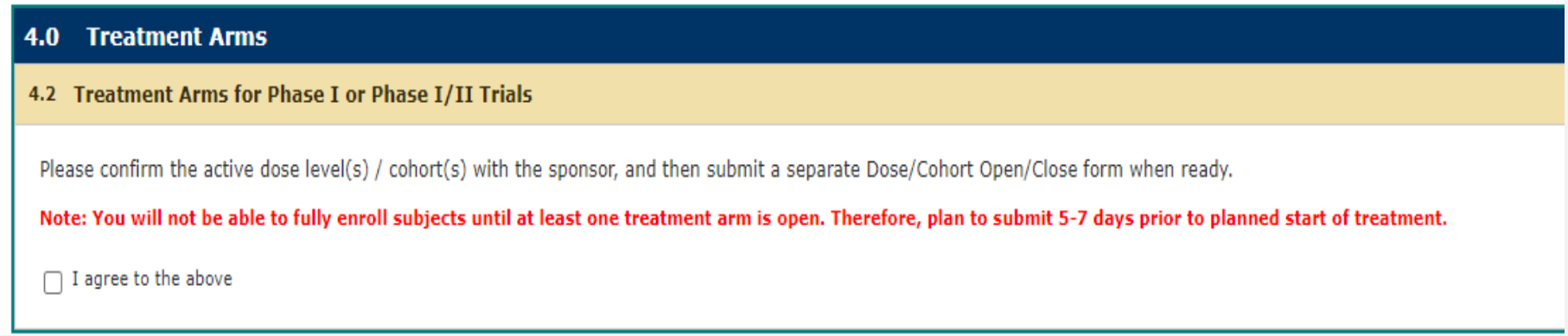
If the NP is activated to a status of **on hold**:

- An **amendment** is required to change the enrollment status to Open to Accrual.
- Dose levels can be opened as part of the amendment.

NP Operational Readiness

The Operational Readiness Checklist (ORC) for phase I and phase I/II trials will be updated.

- You will no longer be able to list cohorts or dose levels on the ORC itself.



4.0 Treatment Arms

4.2 Treatment Arms for Phase I or Phase I/II Trials

Please confirm the active dose level(s) / cohort(s) with the sponsor, and then submit a separate Dose/Cohort Open/Close form when ready.

Note: You will not be able to fully enroll subjects until at least one treatment arm is open. Therefore, plan to submit 5-7 days prior to planned start of treatment.

☐ I agree to the above

This will serve as a reminder to prepare the dose/cohort form.

When should I submit the dose/cohort form?

- The dose cohort form must be submitted **after you have confirmed** with the sponsor the active dose level(s) on which DF/HCC will activate.
- The dose cohort form can be submitted at the same time the NP Operational Readiness Checklist is provided to ODQ, if the active dose level is confirmed.
  - You do not need to wait for the activation notice.
- Plan for a typical turnaround time of 5-7 days for the dose cohort form.

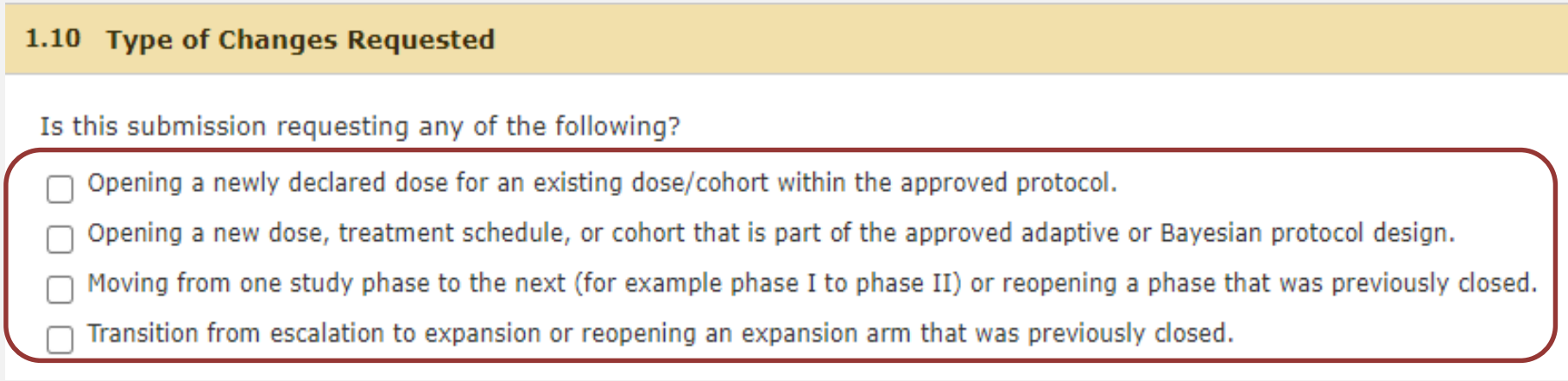
Amendments and Dose/Cohort Forms

- For amendments and dose/cohort forms that open one or more new dose levels, order sets will build and release the new dose level(s) as needed.
  - Amendments with an enrollment status change that request to open new dose levels/arms will now route to Pharmacy Order Sets.

- There are no changes to how you complete the amendment form or dose/cohort form.

Dose Cohort vs. Amendment

Using Dose/Cohort Forms



1.10 Type of Changes Requested

Is this submission requesting any of the following?

- ☐ Opening a newly declared dose for an existing dose/cohort within the approved protocol.
- ☐ Opening a new dose, treatment schedule, or cohort that is part of the approved adaptive or Bayesian protocol design.
- ☐ Moving from one study phase to the next (for example phase I to phase II) or reopening a phase that was previously closed.
- ☐ Transition from escalation to expansion or reopening an expansion arm that was previously closed.

- Dose cohort forms may be used for any of the changes listed here. **Select all that apply.**
- If transitioning phases or from escalation to expansion, the next phase must have been previously approved by the SRC/IRB.
- Please submit as soon as possible after receiving notification from the sponsor.

Requirements for Dose/Cohort Changes

1. Sponsor Correspondence: Pharmacy and ODQ need to verify that the changes we make locally are consistent with what is currently open with the sponsor.
   - Email from sponsor confirming what is open
   - Memo or minutes from a sponsor/DSMC meeting
   - Email from sponsor-investigator if a DF/HCC-sponsored trial

2. Moving to a new phase or transitioning from escalation to expansion require SRC and IRB approval.
   - Attach SRC and IRB memos demonstrating prior approval

SRC/IRB Approval of Additional Phases

SRC and IRB memos began capturing approval of all phases for **new protocols reviewed in January 2021**.

- Protocols that were initially reviewed by SRC or IRB prior to January 2021 will require an amendment to move to the next phase.

The submission has been reviewed and approved by the Dana-Farber/Harvard Cancer Center (DF/HCC) scientific review committee.

The submitted protocol has been approved in its entirety.

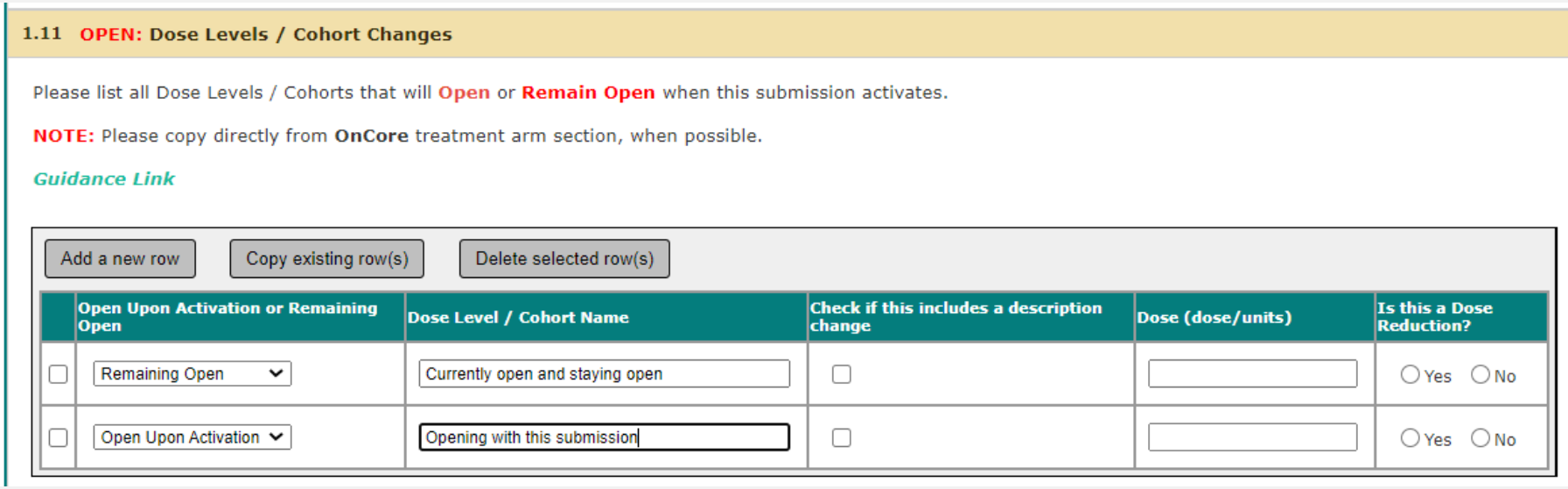
Example of Explicit Approval

The submission has been reviewed and approved by the Dana-Farber/Harvard Cancer Center (DF/HCC) scientific review committee.

Not Approved

The SRC has approved the phase 1b portion of this study. The SRC has noted an amendment that will undergo SRC review will be needed to open the phase 2 study, as there was not sufficient statistical justification for the sample sizes of the phase 2 study or details provided on the randomization.

Important Reminders: Dose/Cohort Forms



1.11 OPEN: Dose Levels / Cohort Changes

Please list all Dose Levels / Cohorts that will **Open** or **Remain Open** when this submission activates.

NOTE: Please copy directly from **OnCore** treatment arm section, when possible.

Guidance Link

Add a new row | Copy existing row(s) | Delete selected row(s)

	Open Upon Activation or Remaining Open	Dose Level / Cohort Name	Check if this includes a description change	Dose (dose/units)	Is this a Dose Reduction?
☐	Remaining Open	Currently open and staying open	☐		○ Yes ○ No
☐	Open Upon Activation	Opening with this submission	☐		○ Yes ○ No

- Sponsor confirmation is required
- **All arms currently open in OnCore must be listed** as either Remaining Open or Closing
- Copy and paste names directly from OnCore to ensure no confusion about what is changing

Strategies for Managing Multiple Amendments

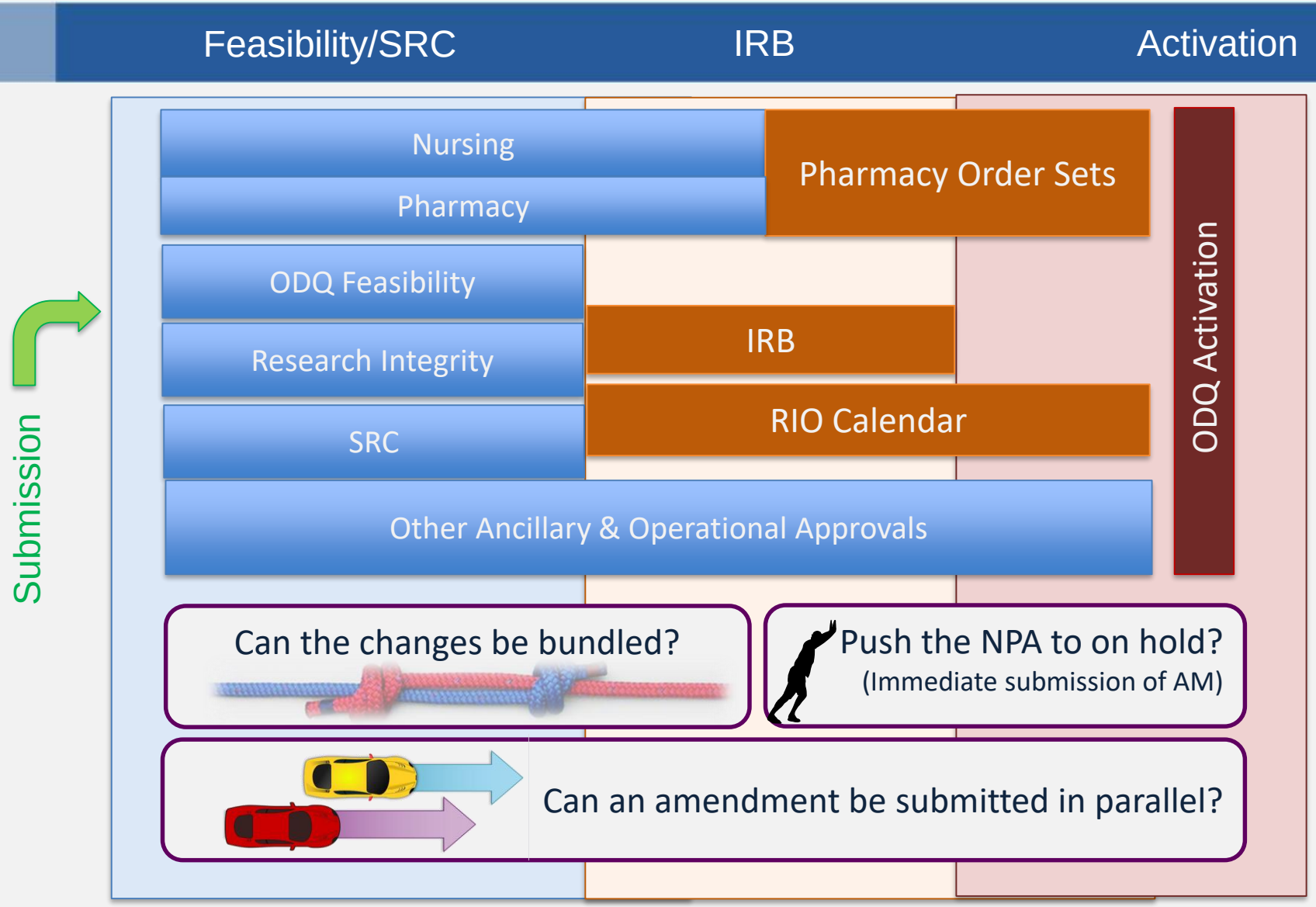
Multiple Amendment Situations

- Contact the iRIS Navigator prior to submitting an amendment if there is already an AM or NPA pending in iRIS.

- We can help you with:
  - Bundling changes into an existing submission
  - Approving a parallel amendment submission
  - Determining the best path to activate new protocols under an amendment

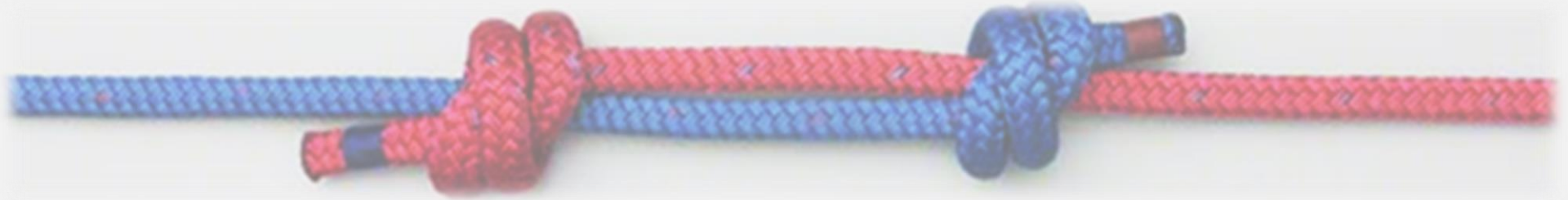
Email: DFHCCiRISnavigator@dfci.harvard.edu

Navigator Strategies



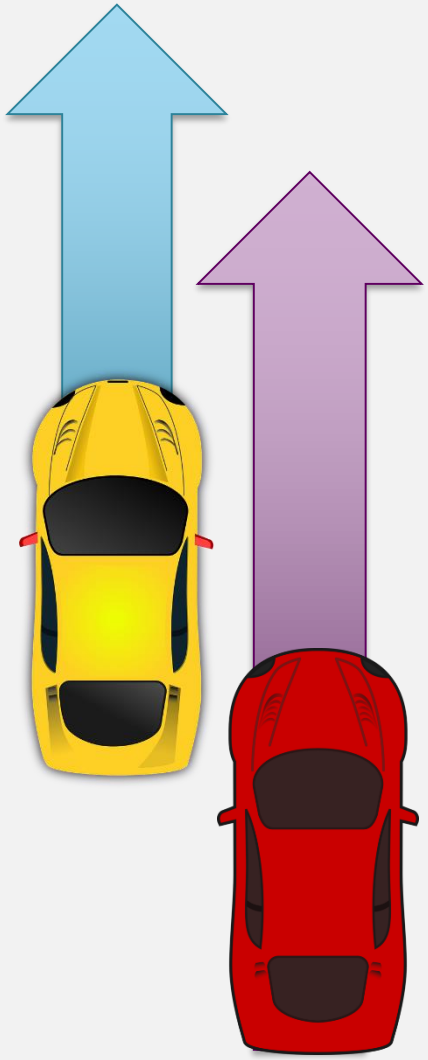
Bundling Changes

- Changes can sometimes be bundled into the pending submission if:
  - The current submission has not yet reached IRB review; and
  - Timing constraints allow for all changes to activate together.
- The navigators will help assess what is changing and what approvals are already complete in iRIS.
  - Bundling may require re-review by some groups.



Parallel Submissions

- May be a better option than bundling if some changes are more urgent than others.
- The navigators will help assess:
  - Any conflicts involving different versions of the same document
  - Any conflicts that could result from updating the core study properties in iRIS on the NPA form
  - Whether order of activation is important.



New Protocols: Activate and Hold

- The Activate and Hold process can save time when:
  - An AM is received while the new protocol is pending activation after IRB approval
  - The AM changes are required to open the study
- The navigators will help coordinate process to allow for immediate submission of the amendment:
  - Bypass pending activation approvals for the new protocol
  - Manually track the pending approvals outside of iRIS
  - Verify those approvals are in place before the protocol is activated in the next amendment