Competing Enrollment and Co-enrollment

Purpose

Enrollment sites may sometimes recruit into two or more clinical trials with overlapping eligibility criteria into which a single patient may be enrolled. The purpose of this document is to provide guidance and expectations for how a site may consider allocating eligible patients among competing trials or when and how co-enrollment may be potentially considered.

This SOP was developed in consultation with the SIREN Human Subjects Protection Working Group and the EFIC IRB Investigator Collaborative.

Definitions

Competing trials	SIREN or external studies with overlapping eligibility criteria in which concurrent enrollment in more than one study is not permissible.
Co-enrolling studies	SIREN or external studies with overlapping eligibility criteria in which concurrent enrollment in more than one trial is permissible.
Allocation	the process by which sites offer or assign enrollment opportunities to patients eligible for competing trials.
Co-enrollment	the process by which sites offer or assign enrollment opportunities to patients in more than one concurrent trial or study.
IRB of Record	the single institutional review board providing approval and oversight for a trial or study. For SIREN trials, this is the ER-CIRB run by Advarra, but another single IRB may be used for competing or co-enrolling trials external to SIREN.
Trial leadership	may be defined by each external trial, but should generally include at least the PIs of the trial, and for SIREN trials also includes the coordinating center investigators.

Responsible Individuals

This SOP describes responsibilities for investigators at SIREN Hubs and Spokes, in the leadership of SIREN Clinical Trials, and at the SIREN Coordinating Centers. It also includes investigators in the leadership of relevant trials and studies external to SIREN.

Process

1. Allocation among competing trials

Enrollment sites that conduct two or more clinical trials with overlapping eligibility criteria should have a plan explaining their strategy for allocating subjects when participation is mutually exclusive.

Allocation strategies: Strategies for allocating patients may consider many factors, including the priority of each trial, the relative frequency of eligibility, the timing of the potential enrollment within the patient's clinical course, patient preference, how many months or years the competing trials are expected to both be actively recruiting, and impact of the allocation strategy on each trial. Possible strategies include, but are not limited to:

- Alternating which trial is offered first based on which trial enrolled last.
- Alternating which trial is offered first based on day, week, or month.
- Always offering the trial with the more restrictive enrollment first.
- Always offering the trial that enrolls earlier in the patient's course first.
- Prioritizing large NIH multisite clinical trials over single site exploratory trials.

Potential for bias: Strategies allocating patients with overlapping eligibility criteria have the potential to introduce bias into whom is enrolled in the study. Minimizing bias is ideal but may not always be practical. Therefore, allocation strategies do not have to be unbiased, but the potential for bias should be considered and managed in every plan.

Trial leadership review: Sites should inform the trial leadership of both competing trials of their allocation strategy. Both trials should accept the allocation strategy. If a trial leadership determines that the allocation strategy will introduce unacceptable bias or otherwise compromise the scientific integrity of the trial, the strategy should be revised or the site should discontinue participation in the trial.

Timing of notification: On SIREN readiness calls, immediately prior to initial site activation, sites should be asked about competing trials. Sites that introduce a new competing trial after site activation should inform both trial leaderships prior to activating the new trial.

2. Co-enrollment among concurrent trials and studies

Sometimes patients may potentially enroll in two or more concurrent trials or studies in which eligibility criteria overlap but in which enrollment is not mutually exclusive. Enrollment sites wishing to co-enroll patients in two or more studies should have a plan for managing co-enrollment.

Co-enrollment considerations: Sites wishing to offer enrollment in multiple concurrent studies to a single participant or their legally authorized representatives should consider multiple factors including any potential interaction between the two studies that might introduce additional risks contraindicating co-enrollment, the additional burden to the patient or legally authorized representatives (LARs) of either

being offered or of participating in both studies, and the potential for co-enrollment to adversely affect the operations, data collection, or scientific interpretation of either of the studies being offered.

In general, co-enrollment is most likely to be scientifically acceptable when one of the studies is an interventional trial and the other is an observational study. Co-enrollment in two interventional studies may be acceptable when one is a usual care study of background care that is uncontrolled in the other study anyway, or when one study has an early outcome that is not thought to be a co-variant in the other study, or where that co-variant is already considered or controlled.

Co-enrollment strategies: When indicated, sites should develop co-enrollment strategies that reduce the burden on participants. These may include coordination between the two studies in approaching patients or LARs for recruitment and consent. Coordination may involve presenting both studies at the same time in a compassionate and coherent fashion that minimizes both confusion and overload, or deliberately staging the two approaches at a deliberate and compassionate interval but with clear descriptions of planned future discussions and expectation management so that the second approach is anticipated and acceptable to the patient or LAR. Co-enrollment strategies should also ensure that follow-up communications and study visits are coordinated so that participants do not feel bombarded by multiple study teams and do not have to return more often than is necessary. If the two studies have overlapping patient reported outcomes or other measures that can be shared, these should be collected once for both trials rather than repeated.

Trial leadership review: Sites considering co-enrollment should inform the trial leadership of both trials of their plan to co-enroll and, if indicated, their operational strategy for doing so. Both trials should accept co-enrollment. If a trial leadership determines that the allocation strategy will compromise the scientific integrity of the trial, or introduce undue risk or undue burden upon the participants, then co-enrollment should not be pursued, and a plan for allocating among the studies should be developed, or the site should discontinue participation in one of the studies.

Timing of notification: On SIREN readiness calls, immediately prior to initial site activation, sites should be asked about potentially co-enrolling studies. Sites that introduce a new potentially co-enrolling study after site activation should inform both study leaderships prior to activating the new study.

Exception from Informed Consent (EFIC): Co-enrollment in two trials that are both enrolling with EFIC can also be considered in this framework but should be considered a special case in which extraordinary efforts at coordination between the clinical trial teams are required. All the considerations previously described including scientific interference and participant burden should still be carefully scrutinized, and both trials still must approve the co-enrollment plan.

In addition, SIREN feels the following parameters should always be followed. The first study team to approach a participant or LAR after enrollment in two trials with EFIC should provide notification and information about both trials. This is relatively straightforward when both trials are conducted by the same study team. If two teams are involved, they can approach cooperatively together, but with consideration as to avoid overwhelming or “ganging up” on the participant or LAR. Alternatively, the teams can cross-train so that one study team member can perform the notification function for both trials. Ideally, that same

notification approach can be used for consent to continue discussions as well for both trials, although well signposted staged consents to continue may also be acceptable and reasonable depending on the specific trials and situations. IRBs should be notified by the trial leadership of plans for sites to potentially co-enroll in more than one EFIC study as described below.

3. Institutional Review Board considerations

If allocation strategies or co-enrollment plans require revisions to a study's eligibility criteria or any other protocol element, then a modification to the IRB application should be reviewed and approved before implementation. In general, however, strategies for allocation to competing trials, or co-enrollment in studies that are not mutually exclusive, are usually already consistent with the IRB approved study protocols and eligibility requirements, and there is no regulatory requirement for these plans to be separately reported to the IRBs of record for either trial or study.

Given the sensitive nature of EFIC research, however, the IRBs of record that approved both trials should be notified by the trial leadership of plans for sites to potentially co-enroll in more than one EFIC study. If there is no change needed to the IRB application or study protocol, this notification should be an informational item and not a protocol modification.

4. Documentation

Each trial should maintain a record of competing and co-enrolling trials and studies by site, and with dates if possible, in a central accessible location, potentially the MoP or a free-standing web document..

SIREN CCC PI Sign-off: Robert Silbergleit Digitally signed by Robert Silbergleit Date: 2025.07.11 16:32:39 -04'00'

SIREN DCC PI Sign-off: Sharon D Yeatts Digitally signed by Sharon D Yeatts Date: 2025.07.11 16:47:57 -04'00'

NIH Administrative PO Sign-off: GRETCHEN C. SCOTT -S Digitally signed by GRETCHEN C. SCOTT -S Date: 2025.07.14 08:41:49 -04'00'