

# Cohorts and Arms and Comparison Groups, Oh My!

Modeling Protocols for Registration and Reporting

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# Some Definitions

Term	42 CFR Part 11	ClinicalTrials.gov	CCR protocol template
cohort	<i>undefined</i>	<p><b>Observational study:</b> group of individuals, initially defined and composed, with common characteristics (for example, condition, birth year), who are examined or traced over a given time period</p> <p><b>Interventional study:</b> <i>undefined</i></p>	a group of subjects who share a common defining characteristic (e.g., a specific disease); the characteristic is known at the time of study entry, and defines the treatments (arms) which will be made available to subjects who have that characteristic
arm	a pre-specified group or subgroup of human subject(s) in a clinical trial assigned to receive specific intervention(s) (or no intervention) according to a protocol	<p><b>Observational study:</b> <i>undefined</i></p> <p><b>Interventional study:</b> a pre-specified group or subgroup of participant(s) in a clinical trial assigned to receive specific intervention(s) (or no intervention) according to a protocol</p>	a specific treatment or intervention (or no treatment/intervention) offered to subjects on the study
comparison group	a grouping of human subjects in a clinical trial that is or may be used in analyzing the results data collected during the clinical trial	no explicit definition, and the term is only really used in the context of observational studies, perhaps as an analog to interventional studies' arms	<i>undefined</i>

# CCR Protocol Template-Specific Definitions

Term	CCR protocol template
randomization	A strategy in which subjects are assigned to arms by chance. By definition, studies with randomization(s) have more than one arm.
stratification	A method of attempting to ensure equal distribution of arms within subgroups of study subjects (strata) during randomization. Stratification aims to prevent characteristics which might influence differences in efficacy from biasing the analysis of efficacy results between arms. By definition, stratification only occurs in randomized studies.
stratification factor	A defining characteristic of a group of subjects, similar to that of a cohort. The difference is that a cohort is a macro-level distinction, and defines which arms are even available to a subject; a stratification factor is only considered after a subject is already in a cohort and is ready to be randomized, and helps ensure that the cohort's available arms are equally distributed within subgroups of subjects.

# Simplest Protocol

**Cohorts:** one

**Arms:** one

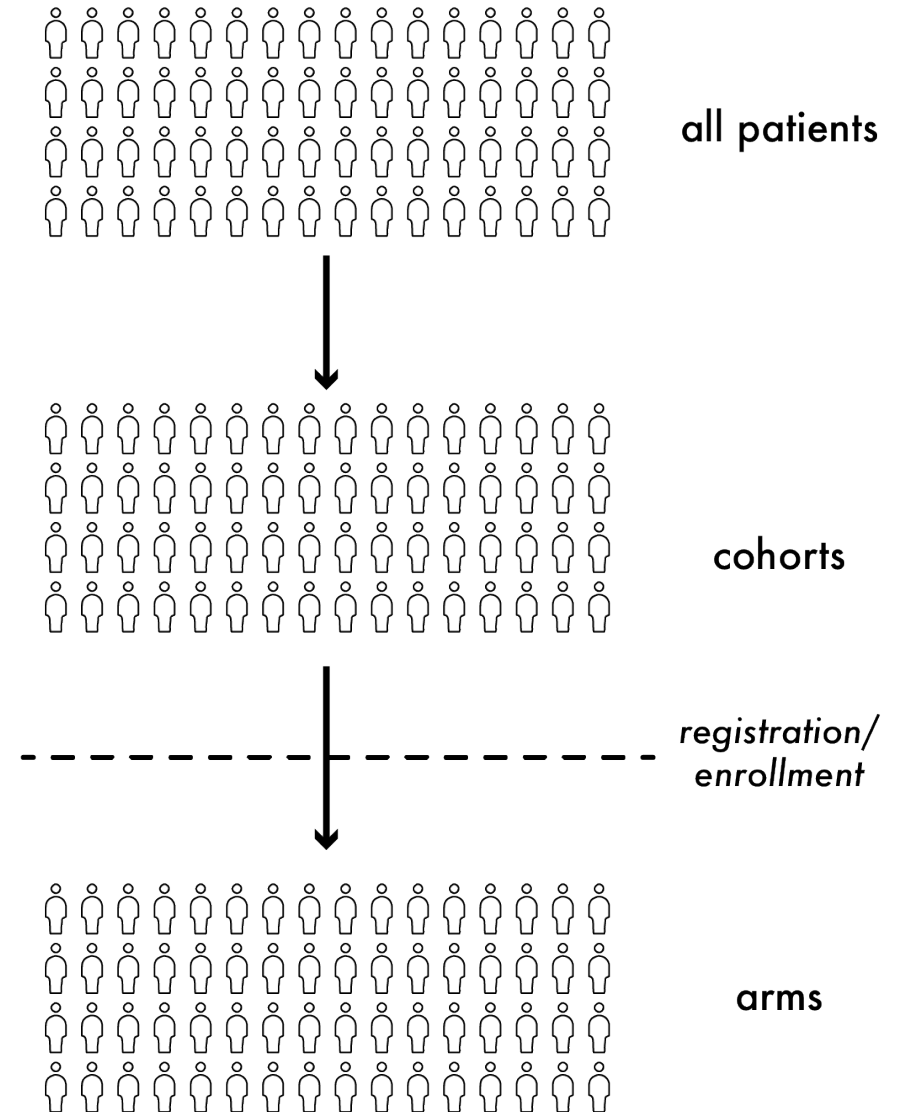
**Comparison groups:** none

All subjects are assigned to a single cohort, and are enrolled in a single “arm”.

**Example:** simple observational study (e.g., a natural history study of a single disease)

## Notes:

- ClinicalTrials.gov only recognizes arms for interventional studies. As a result, we will only define one “arm” for CCR’s observational studies, allowing proper modeling of the fact that subjects all enroll into the same registration bin.



# Addition of Comparison Groups

**Cohorts:** one

**Arms:** one

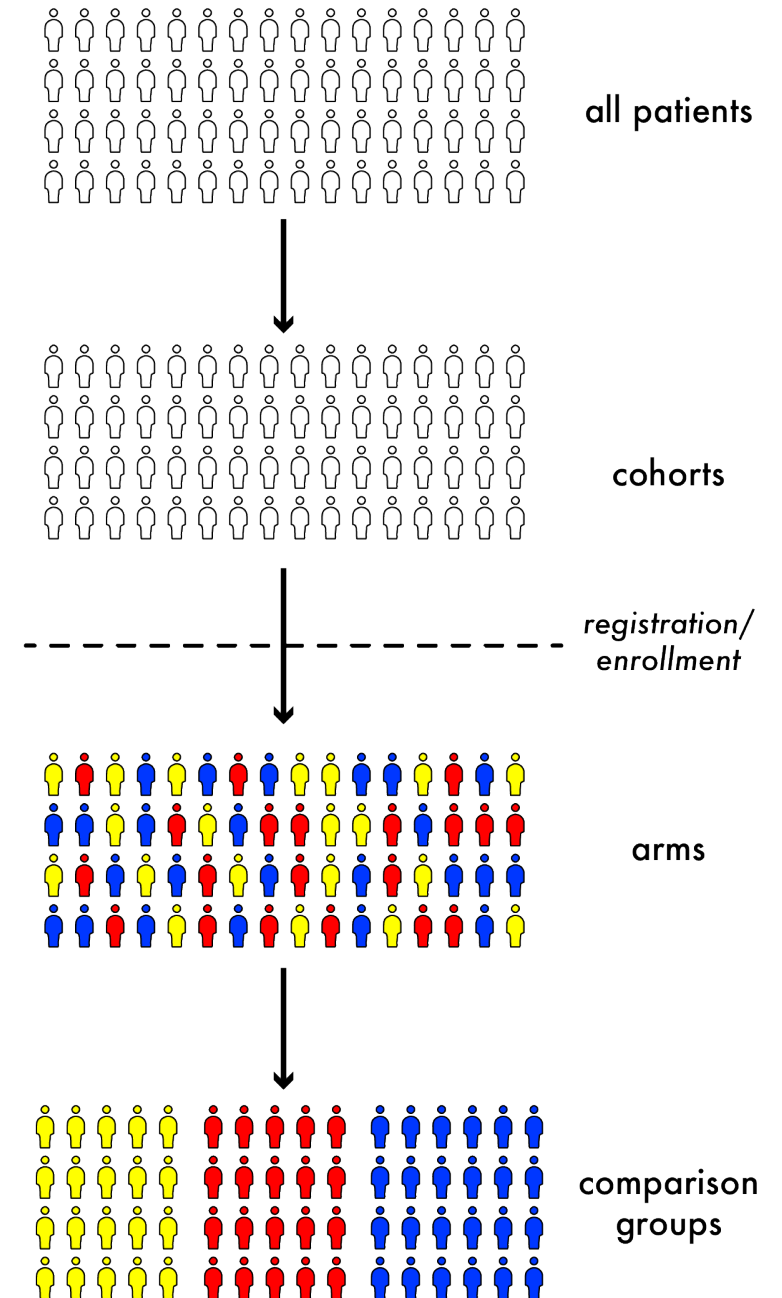
**Comparison groups:** multiple

All subjects are assigned to a single cohort, and are enrolled in a single “arm”. During the course of the study, characteristics of the subjects are studied which define specific subgroups which will be analyzed and reported separately.

**Example:** observational study (e.g., a natural history study of mesothelioma) which includes genetic testing that divides subjects into groups based on a specific mutation status (e.g., *BAP1* mutation)

## Notes:

- Comparison groups are distinguished from cohorts by the fact that the differentiating factor between comparison groups is only learned **after** subject enrollment, but is relevant for the purpose of analyzing and/or reporting results.



# Multiple Cohorts but Only One Arm

**Cohorts:** multiple

**Arms:** one

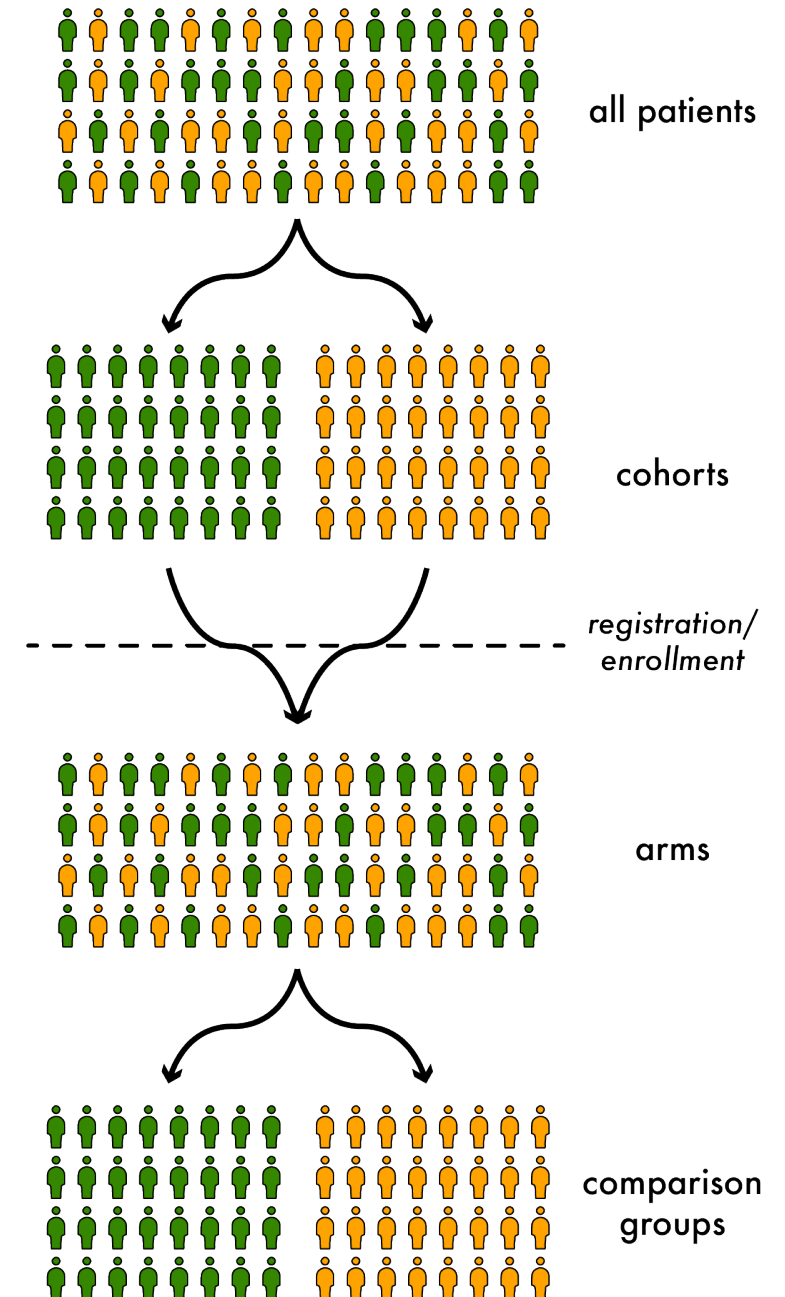
**Comparison groups:** usually multiple

Subjects are assigned to different cohorts based on characteristics which are known at the time of enrollment. Despite the presence of multiple cohorts, all subjects are enrolled in the same arm.

**Example:** phase I interventional study enrolling subjects with distinct diseases (e.g., pre B-cell ALL and T-cell ALL) into the same treatment regimen

## Notes:

- The usual purpose of separate cohorts is to target specific enrollment numbers for each disease; this allows for closing enrollment for one disease while continuing enrollment for another.
- Typically, each cohort is also a comparison group — the study team will evaluate the intervention separately for each disease, and will make comparisons between them.



# One Cohort and Multiple Arms

**Cohorts:** one

**Arms:** multiple

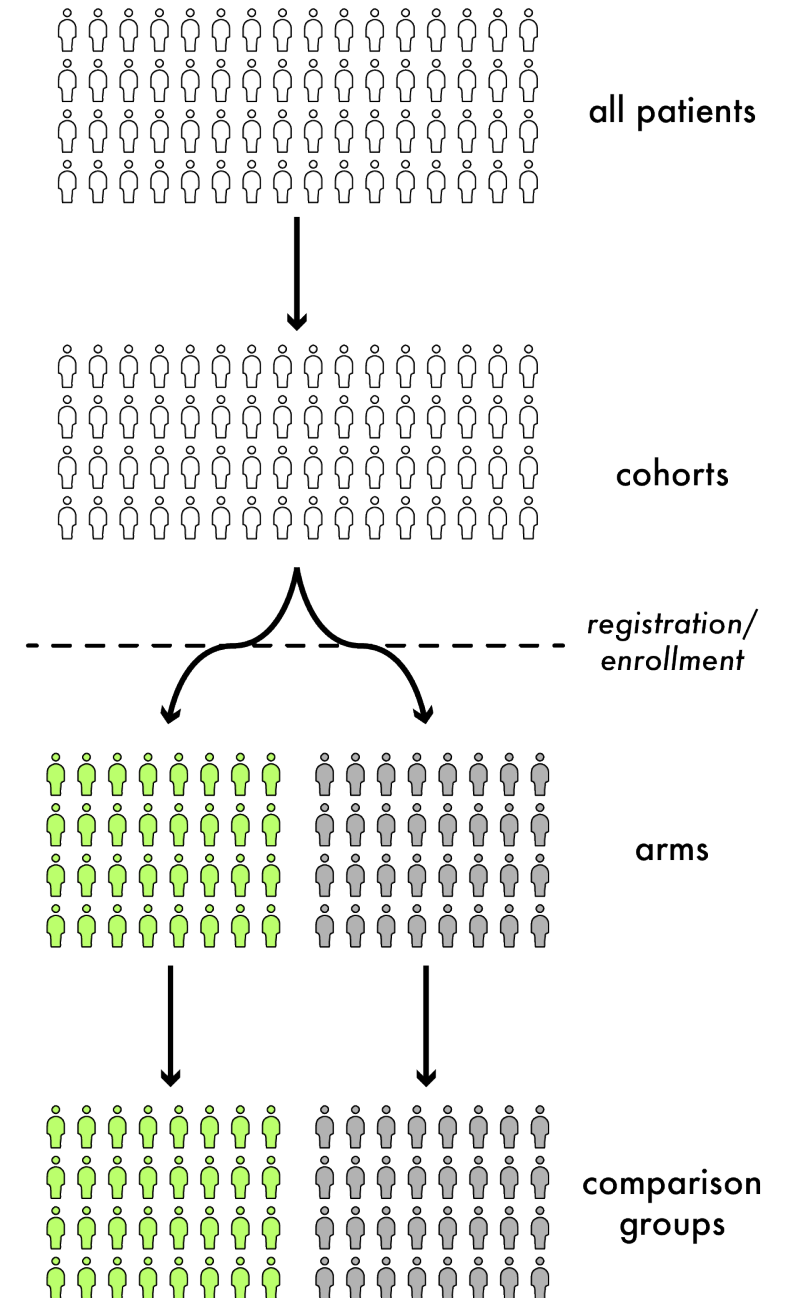
**Comparison groups:** multiple

Subjects are assigned to a single cohort, and then are enrolled in one of multiple different treatment arms.

**Example:** phase III interventional study of a disease (e.g., pre-B ALL), assigning subjects to two different arms based on a characteristic that has relevance to the treatment they receive (e.g., low-risk vs. standard-risk disease)

## Notes:

- Note that the distinguishing characteristic between patients in separate arms is not known until **after** enrollment; in this example, the distinguishing characteristic is the arm assignment, which happens at the time of enrollment.
- Each arm usually defines a comparison group, since the arms will be analyzed and reported separately.



# Multiple Cohorts, Multiple Arms

**Cohorts:** multiple

**Arms:** multiple

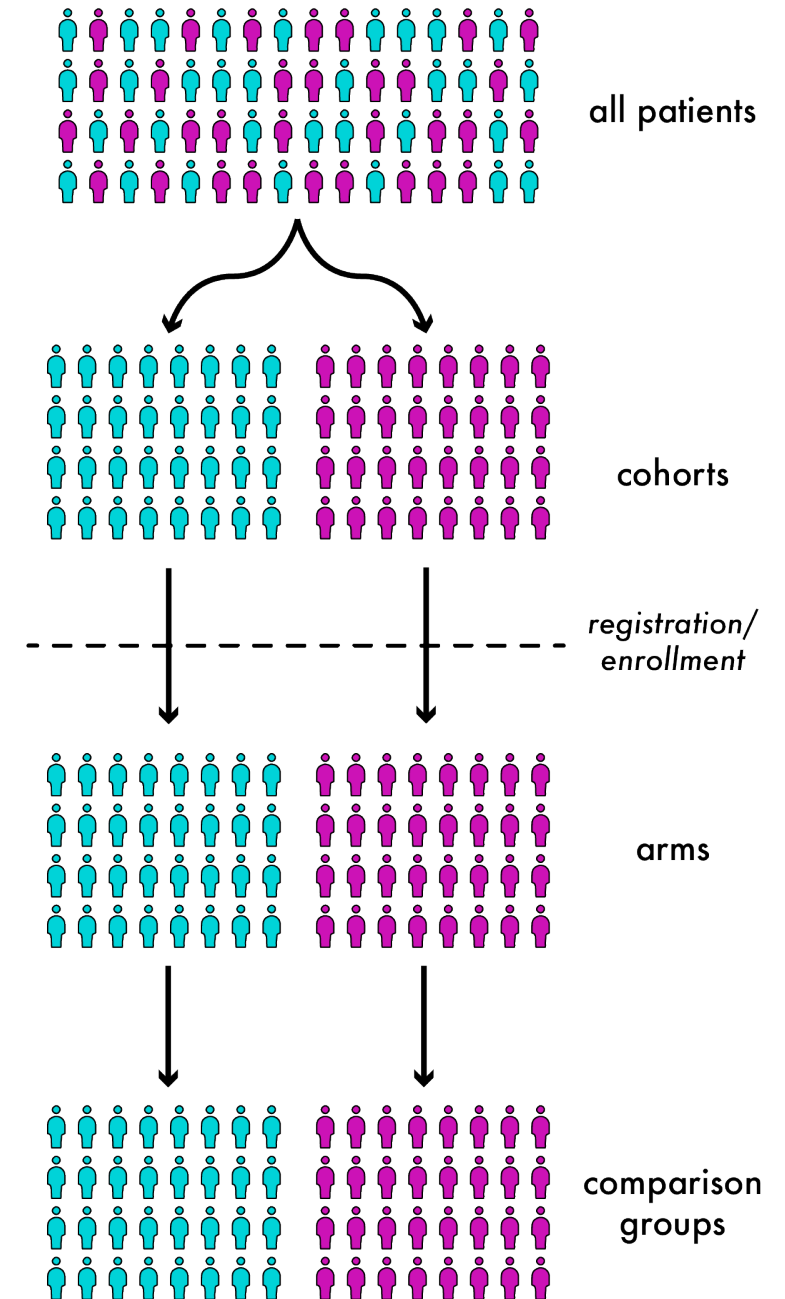
**Comparison groups:** multiple

Subjects are assigned to different cohorts based on characteristics which are known at the time of enrollment. Each cohort is enrolled in a separate treatment arm.

**Example:** phase II interventional study of a set of related solid tumors, treating each type of tumor with an experimental agent (at the phase I MTD) in combination with a standard regimen for that tumor.

## Notes:

- As with the multiple-cohort-one-arm example, there are multiple cohorts defined here to allow for setting target enrollment numbers per type of tumor.





# How does Randomization Fit In?

**Cohorts:** one or more

**Arms:** multiple

**Randomization:** one

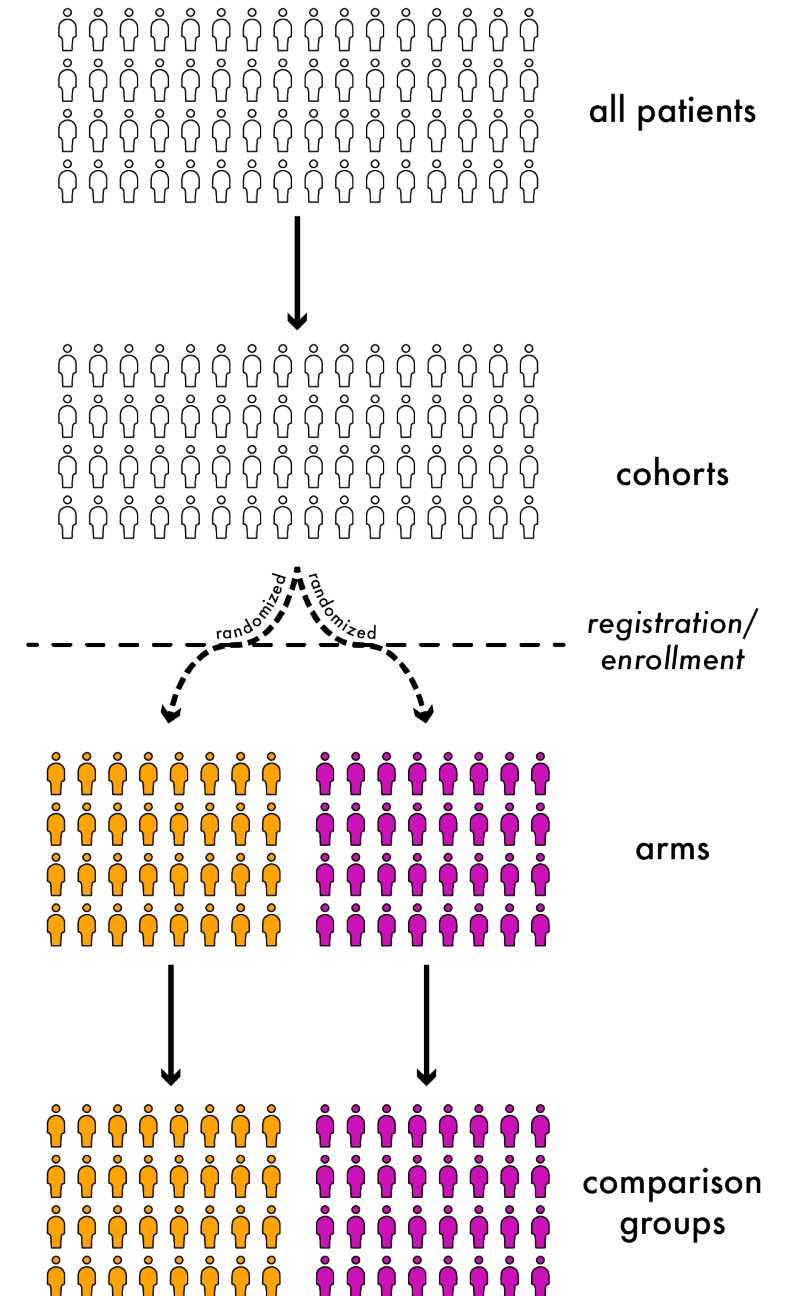
**Comparison groups:** multiple

Randomization is the process by which subjects are assigned to a study arm via chance. Randomization necessarily comes *after* the selection of a cohort; cohorts are linked to a set of arms, and assignment to a cohort's arms is performed via the study's specified randomization method.

**Example:** phase III interventional study of a disease (e.g., pre-B ALL), randomly assigning subjects to two different arms, one representing the standard of care and the other representing an experimental therapy

## Notes:

- This looks nearly exactly like the “one cohort, multiple arms” slide — because the only difference is how the patients in the single cohort are assigned to the two arms.



# OK, What About Stratification?

**Cohorts:** one or more

**Arms:** multiple

**Randomization:** one

**Stratification factor:** one

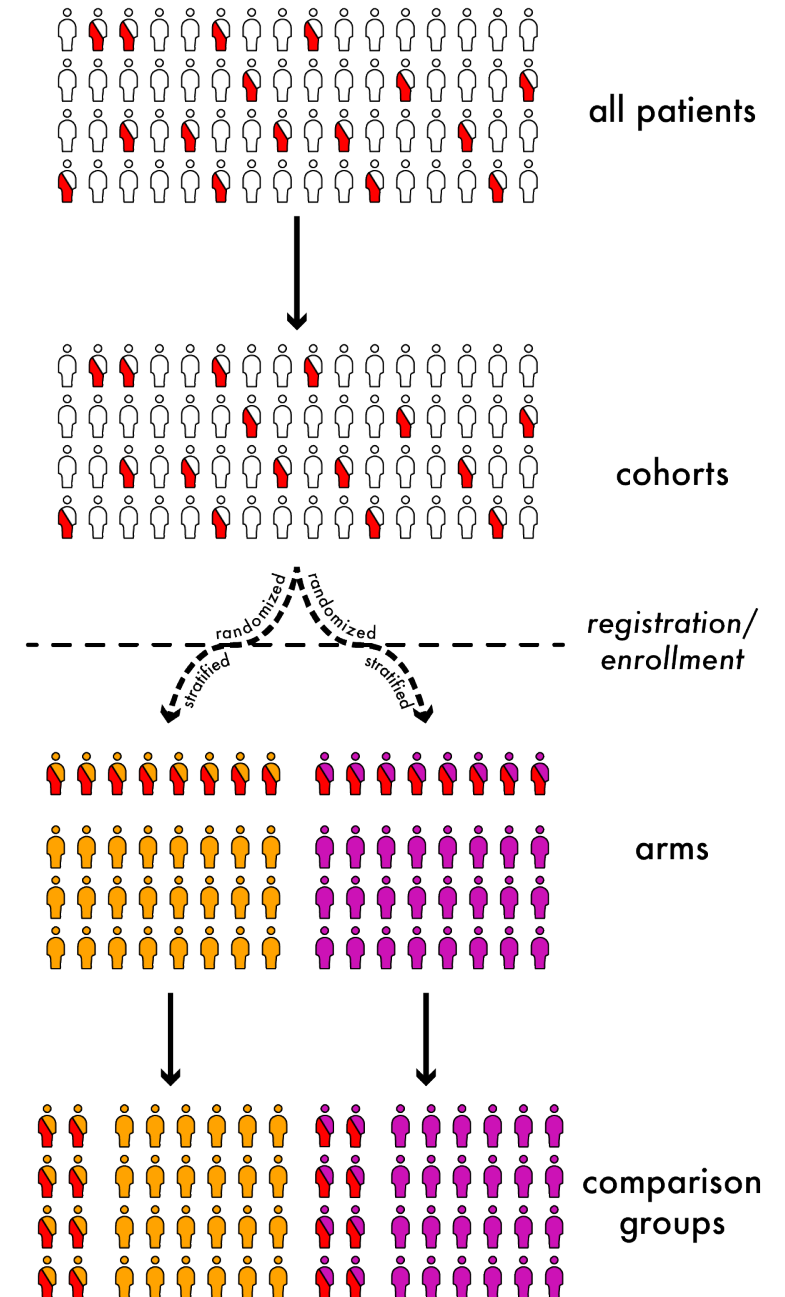
**Comparison groups:** multiple

Stratification involves identifying specific subgroups of subjects, and then performing randomization such that the arms are equally distributed within these subgroups. By definition, stratification only occurs in randomized studies.

**Example:** phase III interventional study of a disease (e.g., pre-B ALL), randomly assigning subjects to two different arms (standard of care vs. an experimental therapy) stratifying for the presence or absence of trisomy 21 (Down syndrome).

## Notes:

- Stratification factors are characteristics which are known prior to enrollment, and are taken into consideration after a subject is assigned to a cohort.
- Stratification factors help assure that a given subgroup of subjects don't end up disproportionately assigned to a single arm of the study.



# It Gets Complicated!

**Cohorts:** multiple

**Arms:** multiple

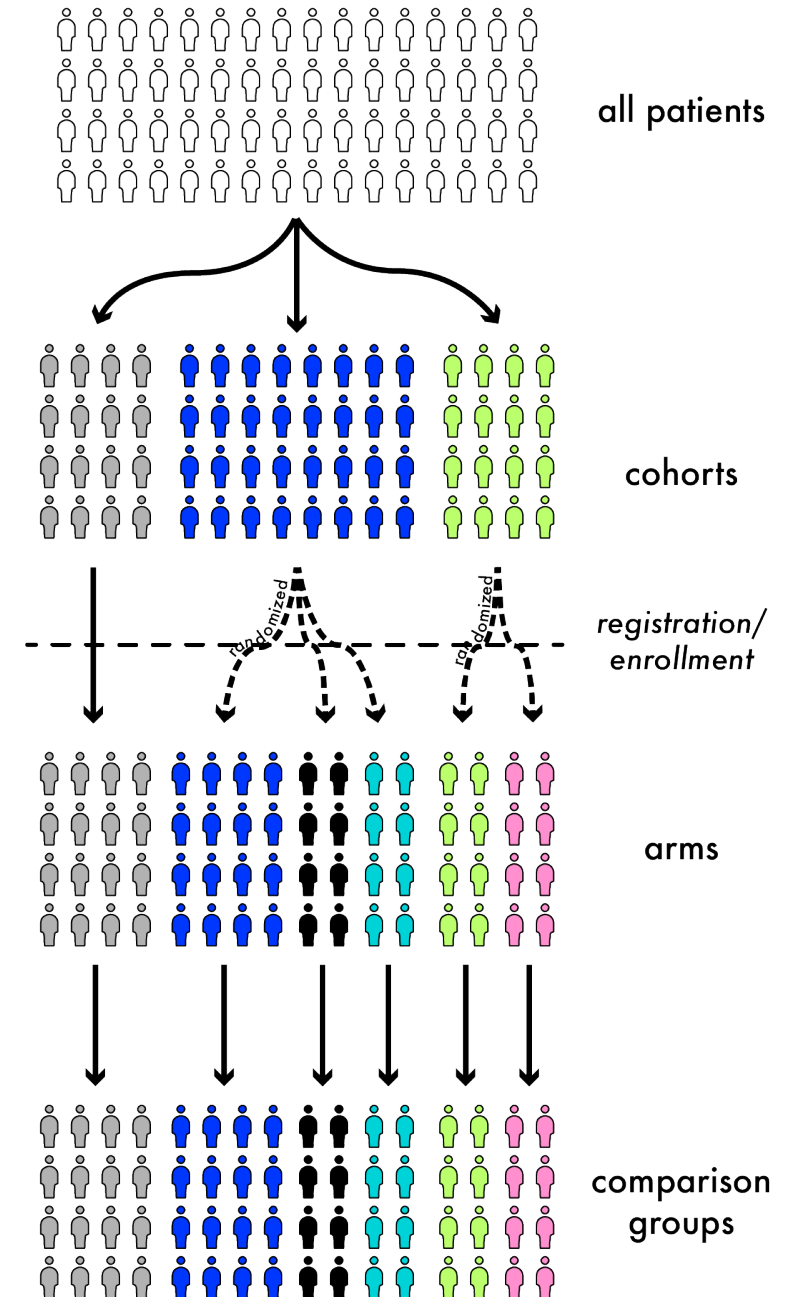
**Comparison groups:** multiple

Subjects are assigned to different cohorts based on characteristics which are known at the time of enrollment. Enrolled into arms occurs according to potentially-different rules for each cohort.

**Example:** phase III interventional study of a set of different diseases, with one cohort being directly-assigned to a single treatment arm, a second cohort being randomized (2:1:1) between three different arms, and a third cohort being randomized (1:1) between two different arms.

## Notes:

- These tend to be our most confusing protocols, but highlight the true reason that cohorts exist — to allow for up-front assignment of a subject into a category (a cohort) that then defines the possible arms into which the subject might be enrolled, and the mechanism by which the arm is chosen for that subject (e.g., direct-assignment, randomization, randomization with stratification, etc.).



# References

- **ClinicalTrials.gov Protocol Registration Data Element Definitions for Interventional and Observational Studies**, <https://prsinfo.clinicaltrials.gov/definitions.html> (dated June 29, 2017)
- **42 CFR Part 11 — Clinical Trials Registration and Results Information Submission**, <https://www.law.cornell.edu/cfr/text/42/part-11> (retrieved November 9, 2017)