

Feasibility Decision Tree

A tool to prioritize the recruitment of a representative population during site selection

Purpose

This tool provides a high-level decision-making framework that can be used by industry or academic **sponsors and/or CROs** during the feasibility assessment and site selection process in order to select sites that can best fulfill the trial's target representative population.¹

The overall objective of a feasibility assessment is to select sites for "optimum project completion in terms of timelines, targets and cost."

Rajadhyaksha, 2010

This tool aims to be

- **Supplementary:** this tool should not work against existing sponsor priorities; rather, the user should embed this tool into their existing site selection methodology.
- **Multi-regional:** the tool can and should be applied to multi-center clinical trials and/or clinical trials conducted in multiple regions or countries.
- **Capacity-building:** in order to facilitate benchmarking of site needs and capacity to enroll diverse populations, this tool incorporates "Checkpoints" where the sponsor/CRO can objectively assess the capacity of a site **and then determine whether enhancement is possible.**

Background

Despite the proliferation of multi-regional clinical trials in recent years, many groups have remained underrepresented in clinical trials globally.² Data generation will inherently vary across countries, for example racial and ethnic diversity applies differently in countries of context, and therefore the variable or data element of interest should be defined in advance of using this tool. In general, this tool is designed to be adapted for application across data elements, regions and countries.

Why Feasibility Assessment and Site Selection?

Clinical trial site feasibility assessment is a decision-making process that traditionally involves evaluating the possibility of conducting a particular trial in a particular region or at a particular site, "with the overall objective of optimum project completion in terms of timelines, targets and cost."¹

These assessments are conducted by sponsors and/or CROs, most often by requesting potential sites to complete a feasibility questionnaire that acquires data on the potential for success of the trial at that site.

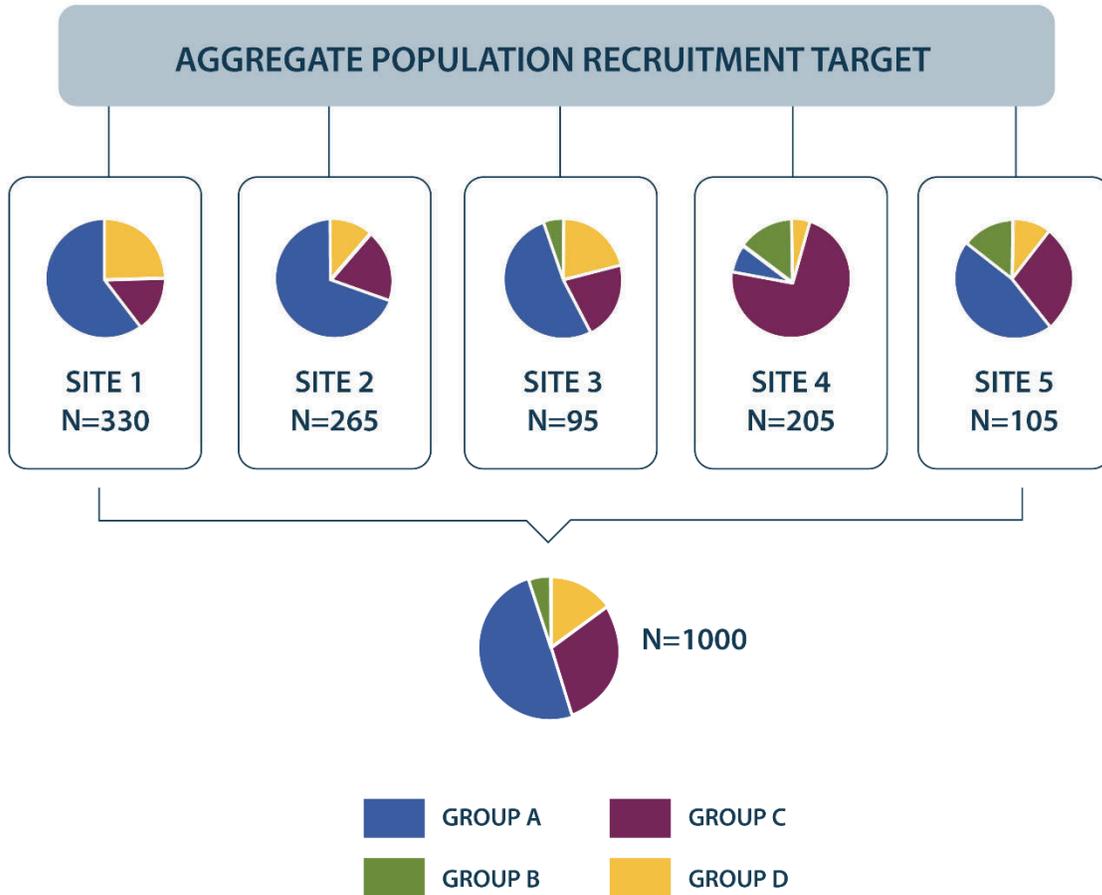
¹ Rajadhyaksha V. Conducting feasibilities in clinical trials: an investment to ensure a good study. Perspectives in clinical research. 2010 Jul;1(3):106.

² Knepper TC, McLeod HL. When will clinical trials finally reflect diversity?.

It is important to note that what matters in a multi-site trial is the **aggregate enrollment of the trial**. Therefore, this tool encourages sponsors to consider the potential enrollment capabilities of representative populations at each site during the site selection process, in accordance with the trial's aggregate target population. For a variety of practical reasons, not every site can enroll a representative and diverse population. As such, this tool provides a framework that can be used to assess the capacity of each site to enroll particular subgroups, addressing the overall strategic goal of achieving a diverse participant population across the study in aggregate. This becomes particularly significant in multi-regional trials where sites themselves are heterogeneous and site selection occurs across countries.

Use Figure 1 below as a visual aid for this concept. To achieve diverse representation in clinical trials in accordance with the MRCT Center's principles around diversity, studies as a whole should include a diverse population. This should be a strategic goal of sponsors and CROs aiming to achieve a population in their trials that is representative of those most likely to use the product in development. However, each site within a study will contribute its unique participant population to the overall study population (i.e., in Figure 1, Sites 1 through 5 each contribute a unique participant population to the overall study population). Therefore, the tool at hand was not built to help select sites that would each achieve diverse representation in their recruited population – a practically unfeasible goal. Rather, the tool was built to help ensure sites enroll particular subgroups at levels that will help the trial meet its strategic goals for diversity and achieve the intended population, based on the epidemiology of the disease. **In this way, the aggregate study population of the trial can achieve diverse representation.**

Figure 1: Unique site contribution to aggregate multi-site trial population achieving representative diversity across a hypothetical trial



Feasibility Decision Tree - considerations for use

It should be noted that in recent years there has been growing emphasis across the clinical research enterprise on the need for objective measures and standardization of feasibility assessments.³ This emphasis is in part due to the traditional overreliance on subjective investigator estimates and feasibility questionnaires, common study delays and the high costs of trials.^{3,4}

The Feasibility Decision Tree tool (see Figure 3: Feasibility Decision Tree - **a tool to prioritize the recruitment of a representative population during site selection**) is structured to offer a comprehensive assessment of a single site's capacity at multiple tiers (*potential, historical, and future*), as discussed below. This tool is intentionally:

1. **Non-prescriptive**, in that it suggests a framework for assessing the feasibility of sites to enroll a diverse population but does not provide specific methods for that assessment. The tool can therefore be adapted to unique clinical operations approach of the sponsor/CRO user.
2. **Non-selective**, in that the framework provides thematic areas, but does not provide fixed criteria to determine a site's capacity for diverse enrollment. In fact, it incorporates multiple "checkpoints," at which the user can reconsider the capacity of a site. This provides flexibility for the sponsor/CRO in their approach to determining the capacity of a site to enroll a desired subgroup into a trial.

The motivation for this framework to be non-selective is rooted in the mission to build industry- wide capacity for diverse representation in clinical trials. Achieving diverse representation across trials will require strong partnerships between sites and sponsors. For this reason, this tool proposes providing feedback to those sites deemed to lack potential capacity for enrolling a particular subgroup. Further, rather than eliminate sites without historical record of enrolling a particular subgroup, sponsors and CROs should attempt to increase capacity within these sites that have potential capacity to enroll that subgroup, by means of providing feasible, evidence- based supports to achieve targeted recruitment. Note that sponsors are expected to provide recruitment materials that are adapted for the specific group and translated as needed, and that site budgets should also allow for a site's unique recruitment efforts.

³Hurtado-Chong A, Joeris A, Hess D, Blauth M. Improving site selection in clinical studies: a standardised, objective, multistep method and first experience results. *BMJ open*. 2017 Jul 1;7(7):e014796.

⁴Johnson O. An evidence-based approach to conducting clinical trial feasibility assessments. *Clinical Investigation*. 2015 May;5(5):491-9.

How to use this tool

This tool establishes three tiers from which to assess sites: *potential capacity*, *historical capacity*, and *projected capacity* (see Figure 2). Each tier, described in more detail below, should be assessed by the sponsor/CRO when determining whether a site ultimately has the capacity to engage a particular subgroup in a clinical trial. Embedded into these tiers are "Checkpoints" that encourage sponsors/CROs to reconsider how sites might be able to achieve capacity to successfully enroll a particular subgroup in a clinical trial (see Table 1).

It is important to note that this tool provides a framework to assess the capacity of a single site in a field that is currently under-addressed in feasibility assessments. As such, we expect that its use will lead to iterative improvement of the tool itself.

We hope that users will share those experiences, specific applications and examples of success and challenge in its application with the MRCT Center (email: MRCT@bwh.harvard.edu).

Figure 2: Capacity tiers as a framework for site selection to promote diversity

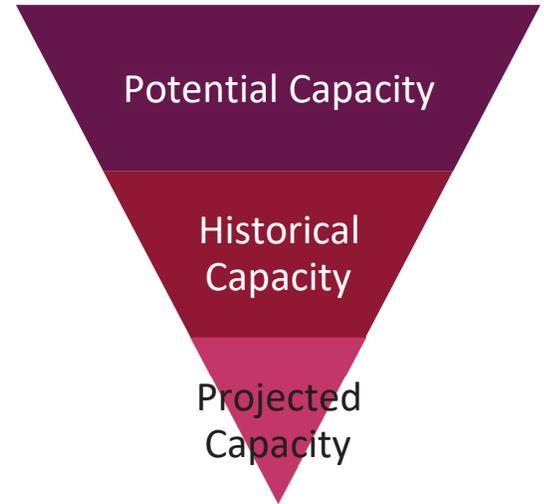
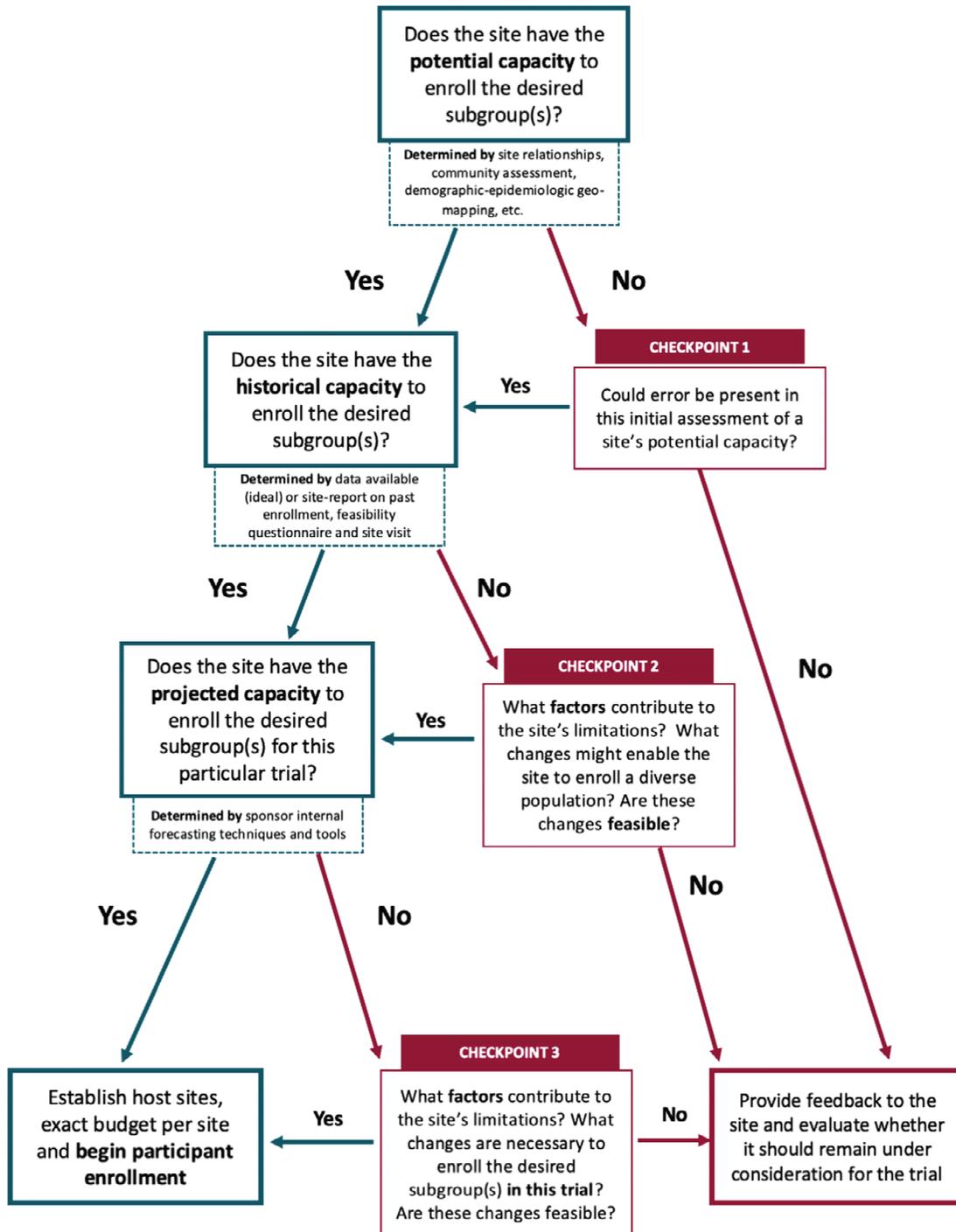


Table 1: Summary of Checkpoints within decision tree tool

Checkpoint	Capacity Tier	Purpose
Checkpoint 1	Potential Capacity	Assessment of methods used to determine a site's lack of "potential capacity" for enrollment of desired subgroup(s). If bias/inaccuracy is detected in these methods, the site remains eligible for consideration in site selection for enrollment of that subgroup(s).
Checkpoint 2	Historical Capacity	Identification and assessment of factors that contribute to a site's lack of "historical capacity" for diverse enrollment, the changes needed in order to build that capacity in the future, and whether supportive measures might be feasible for the sponsor/CRO to provide. If changes are deemed feasible to make, the site remains eligible for consideration in site selection for diverse enrollment.
Checkpoint 3	Projected Capacity	Similar to that of "historical capacity," identification and assessment of those factors limiting a site's "projected capacity" for diverse enrollment <i>in the trial at hand</i> , according to whatever diversity goal and target population established by the sponsor. If identified changes are feasible to make, the site should be included in the study at hand.

Figure 3: Feasibility Decision Tree - a tool to prioritize the recruitment of a representative population during site selection



Assessing potential capacity

The potential capacity of a site can be seen as the **contextual or environmental factors** that contribute to a site's capacity to enroll a particular subgroup in a clinical trial. For example, the site's country, city, geography (urban vs. rural), and/or the demographic composition of the site's catchment area may impact potential capacity. The potential capacity of a site can be determined via existing sponsor relationships with clinical sites, community assessments, and/or geo-mapping of demographic and epidemiological data.

If this initial evidence indicates that a site does not have *potential capacity* to enroll a particular subgroup, the sponsor/CRO reaches "Checkpoint 1," and is encouraged to conduct an internal assessment of the methods used to determine that *potential capacity*. If bias or error is recognized in this initial determination, the site may still be eligible for selection.

For example, potential capacity to enroll particular subgroups can be assessed by determining whether that subgroup is available within the site catchment area (see Figure 4).^{5,6} As such, if the sponsor acquires data from a geo-mapping tool that indicates a particular site's catchment area does not contain a high proportion of desired subpopulation, but that site is in fact embedded

Figure 1: An example of different patient populations at two hospitals within a similar geographic catchment area

In an urban U.S. city, despite sharing similar catchment areas with widely diverse patient populations, two hospitals do not share similar rates of diverse representation in their clinical trials.

Hospital A has a patient population primarily composed of ethnic minorities, while Hospital B has a primarily white patient population. The reasons for this disparity are complex, including:

- **Geography:** more whites live near the Hospital B
- **Cost:** some lower-cost health insurance plans do not cover high-cost care at Hospital B
- **Comfort:** ethnic minorities may not feel comfortable receiving care at primarily white institutions

Of interest is the major racial disparity in clinical trials between the two hospitals – Hospital A hosts significantly fewer clinical trials than Hospital B.⁶ **Because of this, ethnic minorities in this urban city have limited access to participating in clinical trials than whites.**

Applying the proposed feasibility framework, while both hospitals in this case might have the same **potential capacity** to enroll diverse populations in a clinical trial due to a similar catchment area, in reality their capacity is quite different for the reasons demonstrated above. Users of the proposed framework should be aware of these possible nuances and limitations when assessing the capacity of sites to enroll a particular subgroup.

⁵ Johnson O. An evidence-based approach to conducting clinical trial feasibility assessments. *Clinical Investigation*. 2015 May;5(5):491-9.

⁶ Kowalczyk L. Color line persists, in sickness as in health [Internet]. Massachusetts: *Boston Globe*; 12 Dec. 2017 [accessed: Sept. 29, 2019]. Available from: <https://apps.bostonglobe.com/spotlight/boston-racism-image-reality/series/hospitals>.

within a community with ties to the desired subpopulation, their capacity might be higher than predicted. Alternatively, this determination could be biased by factors such as unequitable participant access to trial sites, as well as competition between sites hosting clinical trials in similar indications, in which case their capacity might be lower than predicted.⁷

The motivation of this checkpoint is to be inclusive and ensure that those sites with potential capacity to enroll particular subgroups are not being missed. Further, this checkpoint recognizes that predicting a site's capacity prior to engaging with them or collecting data from them is a known challenge during feasibility assessments.⁸

Assessing historical capacity

The *historical capacity* of a site is defined as the **site's history of enrolling particular subgroup(s)**. Evidence of historical enrollments can be obtained from past enrollment numbers by subgroup, patient population demographics, proof of relationships between the site and community leaders, and/or evidence of an implemented targeted recruitment strategy.

Figure 2: Gender, race and clinical experience (GRACE) case example

GRACE was a phase 3b study designed specifically to enroll and retain women of color for an antiretroviral clinical trial; sponsor-provided support for sites was credited as a major contributor to the success of the trial's engagement of a diverse population.⁹

The sponsor ensured diverse enrollment during site selection by **modifying their feasibility questionnaire** to include questions that ensured:

- **Potential capacity** – sites in areas of high HIV burden among women and people of color
- **Historical capacity** – sites that had a history of actively treating women of color living with HIV, whether or not they had been involved in clinical research before

Sponsor-provided strategic supports included:

- requiring sites to enroll a certain number of women before enrolling men
- hiring community advocates to advise during site selection
- pairing sites lacking capacity for diverse enrollment with more experienced sites for guidance
- granting the engaged CRO special rights to visit less experienced sites and provide technical support

⁷ Rajadhyaksha V. Conducting feasibilities in clinical trials: an investment to ensure a good study. Perspectives in clinical research. 2010 Jul;1(3):106.

⁸ Johnson O. An evidence-based approach to conducting clinical trial feasibility assessments. Clinical Investigation. 2015 May;5(5):491-9.

⁹ Falcon R, Bridge DA, Currier J, Squires K, Hagins D, Schaible D, Ryan R, Mrus J (on behalf of the GRACE Study Group). Recruitment and retention of diverse populations in antiretroviral clinical trials: practical applications from the gender, race and clinical experience study. Journal of Women's Health. 2011 Jul 1;20(7):1043-50.

A sponsor or CRO can collect this information from potential sites via a feasibility questionnaire, modified specifically to generate data on diverse enrollment (see Gender, race and clinical experience (GRACE) case example, Figure 5). Consult the **“Feasibility Questionnaire Modification Checklist”** for a suggested framework on how to approach modifying a questionnaire to increase diverse participation in a trial. Note that empirical evidence has shown that sites and investigators routinely overestimate and overcommit the numbers of eligible participants available and that they are likely to recruit, and this is true prior to any consideration of diverse enrollment.¹⁰ Adopting this multi-tier, rigorous feasibility assessment approach with multiple data sources encouraged by this decision tree tool should help to triangulate on realistic enrollment estimates.

Figure 6: Using Enrollment Prediction Software

If a site is deemed to not have *historical capacity* in enrolling diverse populations, this tool leads sponsors/CROs to "Checkpoint 2," where they are encouraged to consider what changes the site might require to reach capacity and if it is feasible for the sponsor to assist in making these changes. This consideration should be made in active collaboration with site staff.

A software company created a user-friendly, data-driven forecasting tool to help sponsors reach their targeted enrollment on time and on budget. The software allows sponsors to input any data they have (including historical site-specific data) in order to generate accurate predictions of enrollment and recruitment milestones.

A pharmaceutical company uses this tool during feasibility assessments. In an interview, a former director of the pharmaceutical company praised the software in helping "to leverage the actual data that we had...and also to account for uncertainty by incorporating our assumptions... - The result of doing that was a much more thorough understanding of the factors that were driving enrollment."¹¹

Software programs can be used to input multiple data points to predict enrollment milestones, which could include data on the diversity of the expected participant population. Users of this framework could utilize and adapt such tools to aid in predicting a site's projected capacity to enroll a particular subgroup.

¹⁰ Johnson O. An evidence-based approach to conducting clinical trial feasibility assessments. *Clinical Investigation*. 2015 May;5(5):491-9.

¹¹ Cytel. Data-Driven Trial Planning: An Interview with Pfizer's Chris Conklin. Feb. 12, 2015. Accessed February 2020. Available from: <https://www.cytel.com/blog/an-interview-with-pfizers-chris-conklin>

Assessing projected capacity

The *projected capacity* of a site predicts whether a site can enroll the desired subgroup(s) for the **specific trial at hand**. As the considerations for each trial are unique, the sponsor or CRO should use relevant data available for the trial based on the competitive landscape, regulatory requirements, clinical research protocol requirements, recruitment needs, patient demographics, historical enrollments, site requirements and questionnaire-generated data in order to make this assessment. Sponsors can also create an adaptive recruitment plan that is targeted to the specific population and transparent with sites about the goals of these efforts.

In doing so, sponsors and CROs can **adapt existing forecasting techniques** (e.g., software used to generate predictions of enrollment – see Figure 6: Using Enrollment Prediction Software) used during site selection to determine whether sites will be able to engage a diverse demographic in the specific trial being conducted. With the necessary data, utilizing existing software and forecasting tools is a realistic way to assess a site's *projected capacity* to enroll the desired subgroup(s).

"Checkpoint 3" is used for assessing *projected capacity* and is similar to *historical capacity* in that it encourages sites to consider the feasibility of providing support(s) and building site capacity to enroll diverse populations, but in this case specifically for the trial at hand. At this point, a sponsor must determine the level of support available, including financial, to be provided to the site in order to evaluate whether the site should remain under consideration for the trial (see Figure 5: Gender, race and clinical experience (GRACE) case example for further details to estimate budgetary impact).