



# Just-in-Time Site Activation

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An Innovative & Efficient Strategy for Studies  
of Targeted Oncology Therapies

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## Introduction

Today’s targeted oncology therapies have the potential to provide patient benefits far beyond those seen in more traditional treatments. Because they are specifically designed to interrupt signals from the oncogenic driver mutations in tumors, they can deliver much higher objective response rates (ORR), leading to prolonged survival.

These mutations are, however, found only in a small fraction of patients, making it extremely difficult to identify eligible participants for clinical studies. Sponsors who rely solely on the timeworn method of asking sites that have performed well in the past to find patients in any given new study run the risk of drawing out the recruitment phase of their trials and adding substantially to their development costs. Regardless of how detailed the feasibility assessment conducted and how capable the selected sites may be, recruiting patients with required mutations via preselected sites can be like waiting for the needle to jump out of the haystack.

It is, therefore, critical to identify from the outset the most appropriate strategies for recruiting patients, to ensure that valuable time is not lost in inefficient efforts. Just-in-time site activation is an approach that has proven successful in studies of targeted therapies/rare diseases and is worth considering as a solution. The following paper explains how just-in-time site activation works, when it is recommended and what factors determine its success.

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## Shrinking Patient Pools, Growing Enrollment Challenges

The number of patients eligible for study participation (and ultimately for treatment) is inversely proportional to the degree to which a therapy is targeted. For instance, cholangiocarcinoma is already an ultra-rare disease, with about 5,000 new cases in the U.S. each year.<sup>1</sup> Patients with the fibroblast growth factor receptor 2 (FGFR2) mutation make up a only about 15 percent of those.<sup>2</sup> The patient pool for a study in this area would then be further limited by other inclusion/exclusion criteria such as disease staging. In the end, the number of potentially eligible patients could easily be reduced to a mere fraction of the original 5,000 cases of cholangiocarcinoma. A sponsor might have to recruit from an eligible patient pool of no more than 100 patients across the U.S.

Even when the disease in question is not rare, the convention of activating investigator sites and asking them to find eligible patients commonly falls short; nearly half of the time, sites do not deliver the number of patients they expect.<sup>3</sup> Indeed, 11 percent of selected sites never enroll a single patient.<sup>4</sup> In the case of ultra-rare conditions, relying on pre-identified sites almost always fails to produce the required number of patients within the study timeline. Often, it can take a site more than a year to recruit a single patient with a very specific phenotype. Clearly, this setting calls for the application of new strategies. overlap between qualified sites and high numbers of patients. (See Figure 1.)

☞ One solution is to activate sites ‘just in time’ to accommodate patients who have already been identified as potentially eligible for participation. ☞

## Identifying Patients Early in Their Treatment Journey

Studies of targeted therapies most commonly look to enroll patients with metastatic disease at major cancer centers, after they have received initial treatment interventions at a regional or community center. After all, it is at that point (when the disease is actively progressing and aggressive treatment is needed) that investigational therapy is considered. At this stage in the treatment journey, treating oncologists normally want to begin the next phase of treatment as soon as possible, often within a week of the referral. Unfortunately, when this sequence is followed and when potential study participants are only identified upon referral to a large cancer center, *valuable time may be lost, risking treatment delays at the very point when time is of the essence.*

Increasingly, though, sponsors are seeking approval from regulators to study their investigational product in combination with the standard of care as first-line therapy. When this is the case, patients may begin treatment either at community centers or at large academic institutions.

In either case, it is important to identify potentially eligible patients much earlier than is customary—either when they are about to begin treatment in the community or at the point of referral for the next line of treatment. The ability to do this depends on two things. First, the necessary biomarker screening needs to be performed as part of the patient’s initial workup. (Many thought leaders believe this should be done even before more targeted therapies are considered.) Secondly, there needs to be a way to continue to track identified patients along their treatment journey so they may be approached about study participation at the appropriate time. Identifying patients upon diagnosis and tracking their treatment journey is not yet common practice, but there are large provider networks where this occurs, as discussed below.

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## Just-in-Time Recruiting Methods

There are essentially two basic strategies for quickly finding sites that have access to those “needle-in-a-haystack” patients. Both avoid the expense and redundant efforts involved in activating sites that are never able to enroll patients. Rather, they involve activating sites “just in time” to accommodate patients who have already been identified as potentially eligible for participation.

**1) Accessing Provider Networks.** In the U.S., and to a lesser extent globally, various third-party vendors have contracted with networks composed of several hundred providers to serve as investigator sites. The member sites in these networks, in effect, are pre-registered and have agreed to:

- Make their patients available for clinical trials as they become available
- Accept the payment terms in pre-negotiated contracts
- Adopt executed master Confidential Disclosure Agreements (CDA)
- Abide by executed master Clinical Trial Agreements
- Use a central Institutional Review Board (IRB)
- Use standardized informed consent forms (ICFs).

In other words, the member sites have completed many of the preliminary steps necessary to take part in studies and are, in effect, on standby until a study opens for which they have a prospective patient. (Note: This is different in concept and scale from having a few “backup” sites that can be activated should patient enrollment flag with selected sites.) When a study opens, all sites within the network are instructed to interrogate their electronic health records to identify patients who meet the eligibility criteria, including specific molecular selection criteria. Should a patient be flagged in the system, the site can be formally activated within a matter of days, since the necessary agreements are already in place and ethical reviews can be expedited. Thus, the patient can be enrolled and treated almost at once. Furthermore, since all sites in the network are made aware of the study, any new patient identified during the course of the study may also trigger activation of the site.

☞ The appropriate strategy should be selected upfront, before the protocol is finalized. ☞

**2) Directing Prospective Patients to a Call Center.** Advertising can be targeted to sites, creating awareness of available studies and the characteristics of the patients sought, and instructing them to contact a specially staffed call center. In this way, sites are able to self-identify as being interested and as having identified a potentially qualified patient. The call center staff follow a script to determine site eligibility and, subsequently, patient eligibility. If eligibility is confirmed, the site is put on the fast track to activation. After activation, these sites may continue to screen and enroll additional eligible subjects without having to contact the call center.

The value of just-in-time site activation cannot be overstated. For example, if the overall estimated enrollment rate for a study is expected to be 0.1 patients per site per month, and 200 patients are required, it could take 83 sites 24 months to complete recruitment using a standard approach. Using a network or a call-center approach that reaches 200 sites with potentially eligible patients can facilitate similar enrollment in perhaps 12 to 18 months, while controlling the incremental increase in the number of study sites. In the end, the number of sites may be only slightly more than may have been originally planned, and the final operational cost may be neutral between the approaches due to the increase in the study footprint. But what is far more significant is the fact that the study timeline can be slashed. The opportunity value of getting a drug to market six to 12 months sooner is millions of dollars per day.

### Working with Study-Naïve Sites

A site that comes forward as a result of advertising may lack experience in conducting clinical research. If this site is valuable due to its access to patients and has the necessary infrastructure (facilities, equipment and personnel), it is possible to provide the site with extra training and support via an onsite study coordinator to prepare it for participation. (This support may be provided by a CRO or a third party.)

Working with study-naïve sites requires extra care to:

- Ensure that sites truly understand the target patient profile
- Clearly explain what will actually be required in conducting the study
- Ask very specific questions about the site’s capabilities and facilities to ensure that nothing is assumed
- Be prepared to provide ancillary support for additional equipment or staff required to support the study

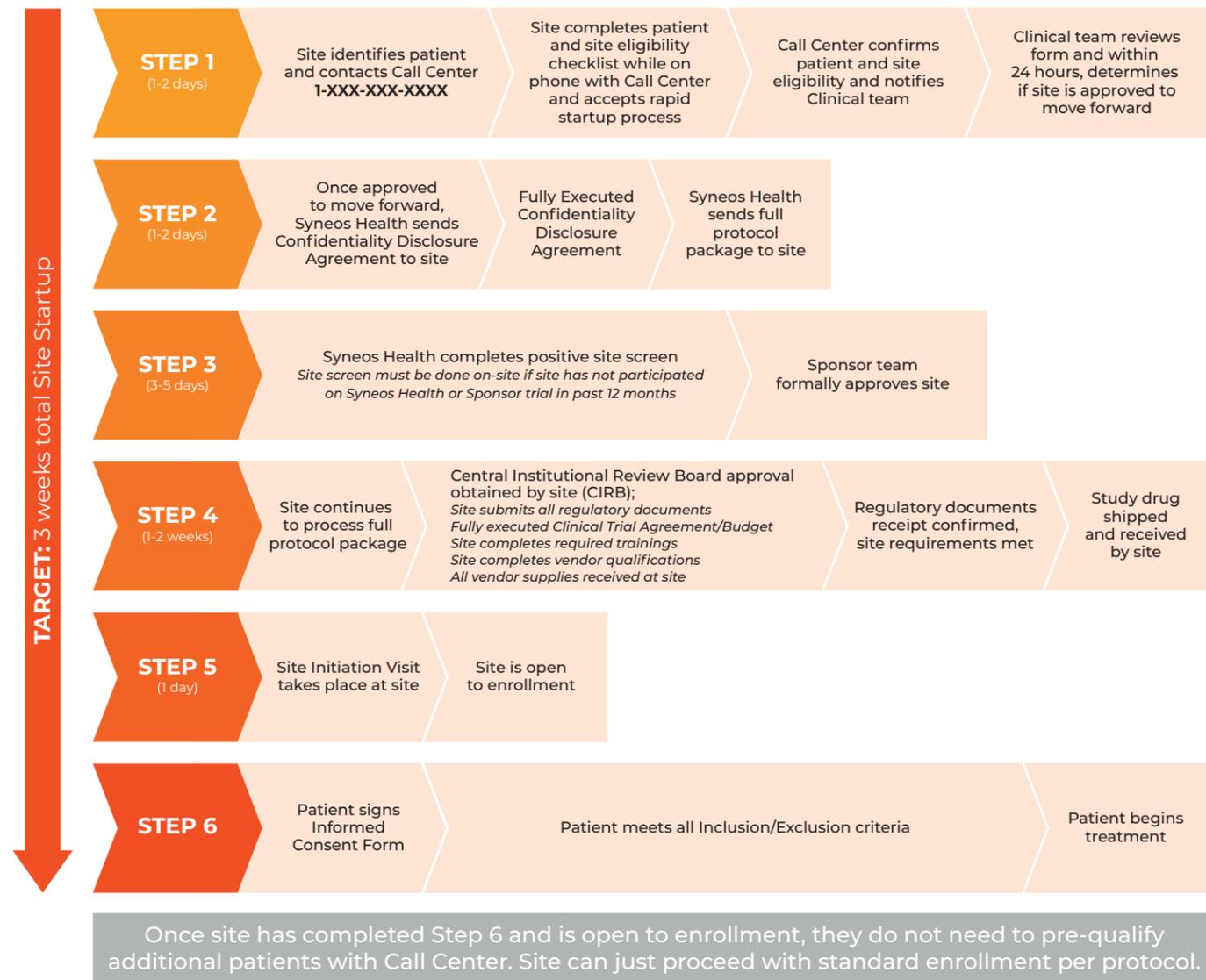
## Rapid Study Startup

There are many steps required to take a site that self-identifies via a call center to the Site Initiation Visit (SIV); some can be completed in parallel, while others must be completed in sequence. When these are carefully orchestrated, as illustrated in Figure 1, the study startup timeline can be reduced to a total of three weeks—a vast improvement over the industry average. One study found that it takes almost eight months, on average, after site identification to complete the study startup phase and be ready to enroll patients.<sup>5</sup>

**Figure 1: Rapid Study Startup Process**

### Initial Patient/Site Startup Timeline\*

Must fully complete each step in succession. Step 3 can occur simultaneously with Steps 2 and 4.



\*Assumes business days

The suggested process for activating a site that has self-identified via a Call Center can be completed in as little as three weeks.

## Selecting the Right Strategy, at the Right Time

Just-in-time recruitment approaches *are only one method of finding/reaching patients*. Indeed, recruitment strategies can be viewed as stretching along a continuum, ranging from direct-to-patient appeals at one end to broad outreach to physicians (as discussed here) at the other end. Many elements can be combined, as befits the challenge and depending on the phase of the research, the number of patients needed compared to the eligible patient population, the complexity of the protocol and the footprint of the trial.

The important thing is to select the appropriate strategy upfront, before the protocol is finalized. The recruitment strategy and the protocol will need to be compatible, ensuring that the specified patient screening requirements do not interfere with a just-in-time approach. If, for example, a very onerous screening process adds substantially to the screening timeframe and extends beyond the window deemed medically acceptable or precludes self-identifying community-based sites from participating, a just-in-time strategy will not work.

What sponsors should avoid is shying away from a just-in-time strategy only to realize much later that they must implement it as a rescue strategy.

### Rapid Study Startup Using Call Center Model

A top-tier, global pharmaceutical company turned to Syneos Health to implement a just-in-time site activation strategy for its trial in breast cancer—specifically targeting men and postmenopausal women with hormone receptor positive (HR+) HER2-negative (HER2-) advanced breast cancer (aBC) with no prior hormonal therapy for advanced disease. This strategy was designed to be implemented in combination with the conventional/traditional site startup model in order to offset the risk. Out of total 82 sites selected for the optimal enrollment, 27 sites were activated through the JIT strategy and 55 sites were activated via the conventional site-startup method. The fountain head of implementing the just-in-time site activation strategy was a protocol-specific, dedicated call center that was set up to field calls from sites that had been exposed to advertising about the clinical trial. The protocol was patient friendly and the site had to accept certain requirements: the use of a central IRB and a standard contract, budget and ICF.

The average study startup time observed for all sites activated under the JIT strategy was about 32 calendar days, with the fastest site activated in six days of first call to the call center, and the sites activated through the JIT strategy accounted for 41 percent of the overall trial enrollment. One-hundred percent of these “JIT-Sites” enrolled at least one patient as compared to only 75 percent of sites activated through conventional site startup method and enrolling via traditional methods.

## Conclusion

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Patient recruitment into clinical trials is often challenging even in the best of circumstances but is especially difficult for studies addressing rare diseases. One solution to avoid activating unproductive sites is to employ a just-in-time activation strategy once potential patients are identified. Its success depends upon the abilities of a Sponsor or CRO partner to capitalize on relationships with third parties who can engage provider networks, perform digital analytics, train treatment naïve sites and draw upon their experience with the just-in-time approach.

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### About Syneos Health

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