

TIME Trial™ Program

INTRODUCTION

Modernization of clinical trials is a focus of the entire healthcare ecosystem; so much so that the FDA has designated it “an agency wide priority” (U.S Food & Drug Administration, 2019). This modernization can take many forms including changes in research design; leveraging larger datasets and increased computing power; and developing new frameworks of collaboration between health care providers, industry leaders, and regulatory bodies. The advent of precision medicine and biomarker targeted therapies has made this need for clinical trial modernization more timely and urgent. A study of 150 clinical trials and nearly 16,000 study sites found that 11% of research sites fail to enroll a single patient and 37% of sites fail to meet enrollment goals (Tufts Center for the Study of Drug Development, 2017). In particular, recent oncology studies have shown that less than 5% of cancer patients ultimately enroll in a clinical trial and less than 20% of patients are matched to genomically-relevant clinical trials (Morash et al., 2018; Basnet et al., 2017). As more and more trials require specific biomarkers, which are by definition rare, enrollment targets will become harder to achieve without modernization efforts.

Tempus has a CAP/CLIA-certified next-generation sequencing (NGS) lab and advanced analytics platform capable of identifying biomarker targets. Leveraging integrated analyses of clinical and molecular data can help overcome some of the challenges of modernization. A recent publication in *Nature Biotechnology* demonstrated comprehensive genomic analysis of clinical data and paired tumor-normal genomic data is capable of matching over 90% of cancer patients to targeted therapies and over 75% of patients to biomarker-based clinical trials (Beaubier et al., 2019). In 2019, Tempus launched its TIME Trial™ program to identify eligible patients and bring trials to them using a just-in-time activation model. This patient-centric program enables a trial site activation on behalf of an identified patient within two weeks.

The TIME Trial™ program is intended to be mutually beneficial for all stakeholders in a clinical trial: patients, providers, and industry partners. For patients, the program increases access to molecularly targeted trials and novel therapies. It also enables patients to continue treatment with their current care team instead of referring out to a different facility, potentially far from home. For providers, the program increases their portfolio of treatment options, while decreasing the effort required to maintain that portfolio. Research teams can wait until a patient is identified to activate a study, eliminating the effort of maintaining studies which never enroll a patient. Tempus also uses its data analytics and artificial intelligence tools to prescreen patients on behalf of sites, greatly reducing that burden for research staff. Finally, for industry partners, the TIME Trial™ program allows for intelligent, rapid identification of potentially eligible patients for rare trials. This will lead to cohorts filling sooner, shortening the timeline to analysis, and eventually increasing the speed of drug development.

This article outlines how the TIME Trial™ program is designed, including onboarding, pre-screening, and rapid activation processes. The article also presents a case study that highlights each of these processes for one of the TIME Trial™ program's first patients.

SITE AND SPONSOR ONBOARDING PROCESS

On average, the timeline from site identification to patient enrollment readiness at a familiar research site ranges from 21 weeks, for contract research organizations (CRO), to 27 weeks, for pharmaceutical sponsors. When a CRO or sponsor has never worked with a particular site, that timeline increases by approximately 7 weeks for a CRO and 12 weeks for a sponsor. Budgeting and contracting issues contribute to activation failures in 50% of cases, followed by resourcing issues at the site (Tufts Center for the Study of Drug Development, 2017). Through the TIME Trial™ Network, Tempus has re-designed the standard activation model and significantly decreased these timelines. TIME allows research sites to identify a patient and then activate the trial in under 10 days, and removes the risk of never identifying an eligible patient. By using a patient centric model, both pharmaceutical sponsors and research sites save time, effort, and money.

In order to rapidly activate sites, Tempus created a robust onboarding process for both pharmaceutical partners and sites. The onboarding process was designed to perform nearly all of the study-start up efforts prior to activation initiation. Sites and sponsors agree to a standard rate card containing non-negotiable costs for over 300 budget line items required for oncology clinical trials. The standard rate card is used to populate study-specific budget exhibits and is paired with a national Medicare coverage analysis to simplify clinical trial budgeting. The standard rate card is adjusted for local cost of living and benchmarked at industry standards. Thus, the use of a standard rate card to populate budget exhibits between sites and sponsors prior to patient identification and trial activation helps speed up the timeline by eliminating budget negotiations.

All parties agree to an industry-standard set of legal and study conduct terms in a Standard Clinical Trial Agreement (CTA) in order to join the TIME Trial™ network. The CTA terms used in the study-specific contract between site and sponsor streamlines the contracting process. When an eligible patient is identified and the site decides to activate, the CTA is executed with the study-specific budget exhibit. Additionally, regulatory submissions for each trial activation are simplified through the use of a single Central Institutional Review Board (CIRB), Advarra. Each trial in the TIME Trial™ program utilizes a standardized informed consent form (ICF) which was developed in collaboration between Tempus, sponsors, and Advarra. Tempus follows a model similar to the CIRB for the National Cancer Institute (NCI), allowing limited

changes to the ICF in order to expedite the review of oncology trials (NCI CIRB, 2020).

All site pre-qualification activities are centralized and conducted by Tempus' experienced research team. Prior to joining the network and activating a specific trial, site capabilities are evaluated through a comprehensive Tempus site questionnaire and pre-qualification visit. TIME's standard Site Feasibility Questionnaire (SFQ) is completed by research sites to fully understand their patient population and research experience, capabilities, and limitations. All TIME research sites undergo identical site tours based on TIME's site qualification process. Site profiles are formulated for pharmaceutical sponsors to review and approve sites for their trials. This review process powers the TIME matching algorithms to ensure that only patients at capable and approved sites are matched to relevant trials.

PATIENT PRE-SCREENING PROCESS

Over 75% of U.S. oncologists use NGS tests to guide treatment decisions. Of those oncologists, 29.1% reported to use NGS to determine eligibility for clinical trials (Freedman et al., 2018). It is expected that this number will continue to rise. Since the program launched in the summer of 2019, tens of thousands of NGS-tested cancer patients have been screened, and nearly one thousand patients have been matched to a growing portfolio of industry-sponsored, molecularly targeted trials. Once a site joins the TIME Trial™ Network, every patient with a sample sequenced by Tempus is automatically screened for all relevant TIME trials (in addition to standard trials matching which is provided for all sites, regardless of TIME participation). Generally, the samples sent for Tempus sequencing are accompanied by a recent progress note and pathology report. This clinical information is ingested, structured, and used in conjunction with the sequencing results to evaluate patients' eligibility criteria and effectively match them to potential trials.

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Additionally, the TIME Trial™ pre-screening process was built to be agnostic to the source of genomic data, and can include results from other sequencing labs, hospitals' internal genetic panels, and/or other pathology results. For this reason, Tempus has built mechanisms for the submission and analysis of patients whom Tempus did not sequence. The most robust mechanism for matching patients is Tempus' Secure Data Exchange (SDE), which is an automated pipeline that allows for patient clinical trial matching at scale. Furthermore, sites can designate a cohort of patients for analysis, and Tempus can review the eligibility of those patients in real time, including a complete history of the patient's cancer journey. Manual options for data submission are also available for sites that cannot use the SDE, or during the period the SDE is being put in place.

Regardless of the mechanism of data submission, Tempus reviews all available clinical and molecular data during the pre-screening process to make an eligibility determination. Multiple levels of automated and human review are conducted before a match is confirmed. When a match is identified, the TIME team notifies site research staff about the match, and provides a complete inclusion/exclusion criteria report. This report is taken verbatim from the criteria in the protocol, and is informed by the relevant available data. In cases where Tempus has a SDE, this report is an in-depth, high fidelity match based on numerous progress notes, prior therapies, and pathology reports. All data points reviewed by Tempus are noted, along with the source documentation for each of those data points. This report is designed to facilitate the eligibility review process on behalf of the sites, assisting in both the evaluation of the patient's eligibility and in documenting where those data points can be found. In cases where a patient is potentially a future match, for instance, if the patient is eligible on all criteria but has not yet had progressive disease, Tempus provides a "watchlist" to simplify decision-making if/when the research team needs to consider a new therapy quickly. Once the match is provided to the site, the site research staff consider the match, discuss the trial with the patient and their family, and make a decision about potential trial enrollment.

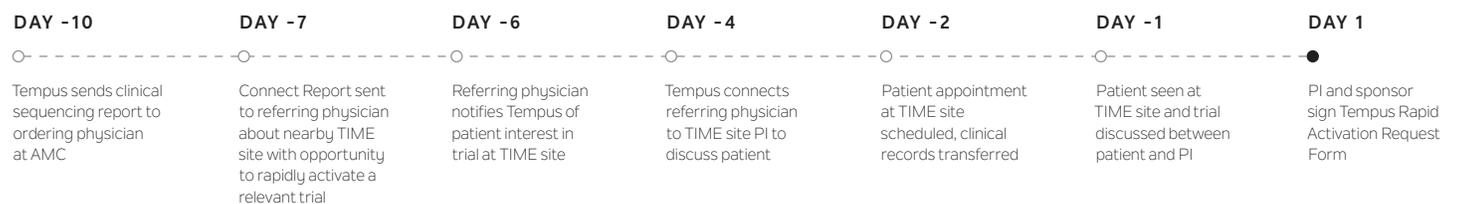


Figure 1. TIME Patient Pre-screening and Referral Process—Case Study Timeline. Timeline showcases Tempus' xT report delivery to the referring physician up through the rapid activation request at the TIME site. The patient was identified as a potential candidate, referred, and consulted within 10 business days.

RAPID ACTIVATION PROCESS

If the site and patient decide to move forward, the site completes the Rapid Activation Request form, which starts the rapid activation process developed by Tempus. This process was designed to take 2 weeks or 10 business days from completion of the form by the TIME site. Since the site is always the final decision maker on whether to open a particular study, the timeline begins once the TIME site submits the Rapid Activation Request. Tempus coordinates the connection and trial activation between the site, sponsor and CRO. Following trial activation, the TIME site continues communication directly with the sponsor and CRO. The site is able to independently accrue patients for the TIME Trial™ program and Tempus continues to support the site in the matching or patient identification process. Below is a case study that highlights both the patient identification and rapid activation processes in more detail.

CASE STUDY

A biopsy sample from a patient with colorectal cancer being treated at an academic center was sequenced and analyzed using Tempus' xT assay. A clinically actionable gene fusion was reported and an open biomarker-based clinical trial was identified through the TIME Trial™ program. Using Tempus' referral network, a notification was sent to the treating physician that a nearby TIME site was capable of running the relevant biomarker-based trial. Tempus connected the referring physician to the TIME site's principal investigator (PI) to discuss the potential trial for that patient. The patient's records were then transferred, and the patient had an initial consult visit with the PI. After the consultation, the decision was made that the best treatment option for this patient was the TIME trial. The referral timeline from when the Tempus xT report was delivered to the referring physician up until the patient's initial consult visit at the TIME site was 10 business days (Figure 1).

The Rapid Activation Request was completed by the TIME site’s PI and the TIME trial sponsor. This action represents Day 1 of the rapid activation timeline. The pre-negotiated CTA and budget exhibit were executed on Day 2 (Figure 2). It was quickly noted that the patient’s insurance was not accepted at the TIME site. The sponsor and site agreed to an all-inclusive budget for study procedures that were not covered by the patient’s insurance. The CTA and budget were executed accordingly within a day. The site-specific CIRB submission was approved by Advarra within 48 hours of submission (Day 5). This approval process was expedited because the site strictly adhered to the ICF template and onboarding process. By the end of the first week, the site had completed all essential documents and submitted them to the CRO. The essential documents were completed and approved by the CRO prior to the site initiation visit (SIV). This also resulted in the approval to release investigational product (IP). The SIV was conducted remotely on Day 8 due to COVID-19 travel restrictions. After the SIV, all activation items were completed and the site activation letter was sent the following morning. The total time from the receipt of the Rapid Activation Request to the clinical trial site activation was 9 business days (Figure 2). The patient consented and completed all screening procedures four days following activation.

Lastly, this TIME site was activated in the midst of the coronavirus (COVID-19) pandemic. Several actions were taken to accommodate the changing clinical trial landscape at this time. For example, an initial feasibility assessment was conducted to evaluate the site’s remote monitoring capabilities. Telemedicine was utilized to conduct the initial consult visit at the TIME site and was investigated as an option for any future study visits to limit the patient’s public exposure. Documents were routed to the PI/ sponsor for signature via DocuSign. All these actions supported the rapid site activation timelines and patient safety during the COVID-19 pandemic restrictions.

FUTURE DIRECTIONS

Tempus is leveraging its NGS testing capabilities, large-scale datasets, artificial intelligence, and TIME Trial™ Network to streamline research efforts in order to advance data-driven precision medicine. As the TIME Trial™ program continues to expand, access to molecularly targeted clinical trials will increase for patients. The program has over 50 active research sites with national coverage, including numerous rural areas which are underserved by large academic centers and the trials they attract. The trials portfolio is growing daily and the process is becoming more efficient each time a new trial is added. As we continue to expand our modernization capabilities and navigate the changing clinical trial landscape post-COVID-19, programs like Tempus’ TIME Trial™ will continue to support the rapid activation of clinical trials, bringing therapies to patients who need it most.



Figure 2. TIME Rapid Activation Process—Case Study Timeline. Timeline showcases Rapid Activation Request form submission through patient consent.

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ABOUT TEMPUS

Tempus is a technology company advancing precision medicine through the practical application of artificial intelligence in healthcare. With the of the world's largest libraries of clinical and molecular data, and an operating system to make that data accessible and useful, Tempus enables physicians to make real-time, data-driven decisions to deliver personalized patient care and in parallel facilitate discovery, development and delivery of optimized therapeutic options for patients through distinctive solution sets. The goal is for each patient to benefit from the treatment of others who came before by providing physicians with tools that learn as the company gathers more data.