PATIENT CARE

original reports abstract

Operational Metrics for the ELAINE 2 Study Combining a Traditional Approach With a Just-in-TIME Model

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PURPOSE There are numerous barriers to enrollment in oncology biomarker-driven studies.

METHODS The ELAINE 2 study (ClinicalTrials.gov identifier: NCT04432454) is an open-label phase 2 study of lasofoxifene combined with abemaciclib in patients with advanced or metastatic estrogen receptor–positive/human epidermal growth factor receptor 2–negative breast cancer with an *ESR1* mutation. ELAINE 2 opened clinical sites by using a Traditional approach, which activated a site before patient identification, and the Tempus TIME Trial network, which opened a site only after identifying an eligible patient. This manuscript presents the operational metrics comparing the Traditional and TIME Trial site data.

RESULTS The study enrolled patients over 34 weeks and 16 sites (six Traditional and 10 TIME Trial) participated. Duration for full clinical trial agreement execution for Traditional sites and TIME Trial sites averaged 200.5 (range, 142-257) and 7.6 days (range, 2-14), respectively. Institutional review board approval time for Traditional sites and TIME Trial sites was 27.5 (range, 12-71) and 3.0 days (range, 1-12), respectively. Duration from study activation to first consent was 33.3 (range, 18-58) and 8.8 days (range, 1-35) for Traditional and TIME Trial sites, respectively. The first patient on study was at a TIME Trial site 115 days before a Traditional site and the first seven patients enrolled were at TIME Trial sites. Traditional sites consented 23 and enrolled 16 patients, while TIME Trial sites consented 16 and enrolled 13. The trial enrolled 29 patients in 8.5 months with the anticipated enrollment duration being 12-18 months.

CONCLUSION The TIME Trial network opened earlier and enrolled the first study patients. These results demonstrate that the Just-in-TIME model, along with a Traditional model, can improve enrollment in biomarker-driven studies.

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INTRODUCTION

The inadequate number of enrolled patients is the primary reason for the premature termination of clinical trials.[1] Barriers that contribute to low recruitment include challenging eligibility criteria that require specific next-generation sequencing results for enrollment. Other factors include trial opening delays from complex regulatory documents, onerous clinical trial agreements (CTAs), and prolonged contractual negotiations.[2] There are also concerns about physician bias in recommending a clinical trial on the basis of a perceived risk-benefit ratio.[3] Patient-level barriers to participation include financial burdens, risk of adverse treatment events, and travel to research locations that are at a significant distance from their home.[2,4-8]

Most clinical trials recruit and enroll patients using Traditional sites, which include large academic medical centers. Once a Traditional site agrees to open a study, a cascade of events occurs. These include budget negotiations, regulatory document completion, local institutional review board (IRB) approvals, and site initiation visits, among other activities. It is common for it to take 6 months or longer to open a trial at a Traditional site, followed by another time lag until the first patient is identified and enrolled.

By contrast, a different method of trial enrollment includes a Just-in-TIME (JIT) approach, where the goal is to rapidly open a trial site once an appropriate patient has been identified. The JIT model partners with clinical sites using a preapproved clinical trials agreement, regulatory process, central IRB, and uniform contracting to allow for a minimal delay in trial activation. Once an eligible patient is identified, the JIT model allows for rapid trial activation at an individual trial site.

We sought to explore the real-time application of one such JIT model, the Tempus TIME Trial, comparing it

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CONTEXT

Key Objective

To determine if the operational metrics for a community-based Just-in-TIME (JIT) research network would outperform academic medical centers for the ELAINE 2 breast cancer study.

Knowledge Generated

The TIME community network used a standard clinical trials agreement, budget, and central institutional review board, which dramatically shortened the duration for trial activation compared with academic medical centers. This head start in opening ELAINE 2 allowed the smaller community TIME sites to enroll similar numbers of patients compared with the large academic medical centers.

Relevance

There is extraordinary pressure for clinical trials to rapidly accrue patients and historically there have been delays in opening up studies at large research institutions. To improve trial enrollments, consideration should be given to also include a community-based JIT network. Additionally, larger academic medical centers need to explore solutions found in JIT models to improve their time to activation as well as overall patient recruitment numbers.

with a Traditional patient recruitment strategy for ELAINE 2, a phase 2 study in patients with advanced or metastatic hormone receptor–positive breast cancer with an *ESR1* mutation (ClinicalTrials.gov identifier: NCT04432454). The primary hypothesis was that the TIME Trial sites would open ELAINE 2 faster than the Traditional sites. Secondary hypotheses included that the TIME Trial sites would consent the first patients, enrollment would be similar between the two groups, no significant differences between data quality would occur, and the combination of using both TIME Trial and Traditional sites would decrease the projected duration of trial enrollment.

METHODS

Patient enrollment for this US-based trial was carried out by using two operational models at Traditional and TIME Trial sites, respectively. The Traditional sites included are academic medical centers that have standard processes for trial activation, patient screening, and enrollment. The study sponsor Sermonix Pharmaceuticals initially approached these Traditional sites to participate in the ELAINE 2 study. Once the Traditional site confirmed interest, multiple steps occurred to activate the trial. These included disease-specific committee review, contract negotiations, CTA approval, regulatory document submission, and local IRB sign-off, among other items.

At the Traditional sites, the study was activated before in-depth screening for eligible patients. Traditional sites relied on their internal processes for patient screening and identification. They used their research personnel to review genomic databases and clinical information to find subjects that matched the ELAINE 2 inclusion and exclusion criteria. Once a potential patient was identified, the appropriate oncologist(s) were alerted and the patient consented to enrollment.

The Tempus TIME Trial program did extensive patient screening before an individual site's ELAINE 2 trial activation using aggregated clinical and molecular data through commercial genomic sequencing and electronic medical record (EMR) integrations. Tempus TIME Trial sites had the ability to integrate their EMR data with Tempus for patient screening before the ELAINE 2 study activation.

Using clinical data abstraction, structured data ingested from the EMR, and natural language processing (NLP), Tempus was able to automatically surface potentially relevant patients for the ELAINE 2 trial. A full description of the NLP process is beyond the scope of this manuscript. However, briefly, the NLP model used predicts whether patients are positive for a specific biomarker. In this case, the biomarker was *ESR1*. The prediction of biomarker status is based on an ensemble of three models: logistic regression,[9] bidirectional long short-term memory,[10] and convolutional neural networks (CNNs).[11] The models are based on past work on using CNNs for sentence classifications.[12,13] These were trained on data comprising a collection of biomarker-relevant context snippets. The patient-level truth labels were annotated by an abstraction team on the training set, following guidelines defined by clinical subject matter experts.

Data screened for eligibility included patient location, age, sex, stage, tumor type, pathologic findings, and next-generation sequencing results, among other items (Fig 1). If a subject met specific eligibility criteria via the NLP model, the patient was flagged for Tempus Staff review against the trial's inclusion and exclusion criteria. Patients deemed potentially eligible were then forwarded to the TIME Trial site's primary oncologist and care team for further review and presentation of the ELAINE 2 trial to the patient as appropriate.

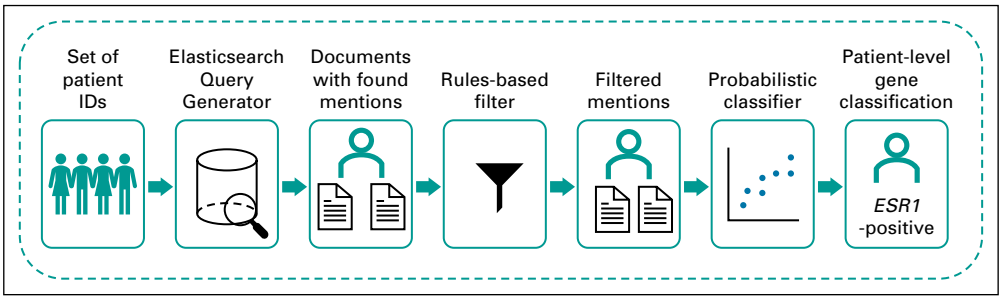

FIG 1. A representative workflow that highlights the processing steps and model output to determine biomarker status.

TIME Trial sites can open clinical trials rapidly using a prenegotiated rate card, uniform CTA, and a single central IRB to streamline regulatory submissions. There were no requirements for a separate TIME site-specific scientific review before opening the study. Additionally, a web-based portal for each TIME Trial site allowed potential future patients to be tracked for impending study eligibility.

A series of comparisons were made of the operational metrics of the Traditional and TIME Trial sites. These data included the length of time for IRB approval, full execution of the CTA, and study activation duration for a site's first consent. Also captured is the total number of patients each site enrolled, race, screen failures, and the date of each enrollment. All data were analyzed using GraphPad prism software version 9 (GraphPad Software, Inc, San Diego, CA).

RESULTS

The first patient was enrolled in 2020 and the last patient was enrolled in 2021, which occurred during the COVID-19 global pandemic. The clinical results from ELAINE 2 have been presented.[14] A total of 16 sites (six Traditional and 10 TIME Trial) participated. All Traditional sites, and none of the TIME Trial sites, were affiliated with major academic institutions (Fig 2). The total number of patients prescreened was not tracked at Traditional sites and therefore is not available. At TIME Trial sites, over 52,000 patients were prescreened via an automated process using genomic sequencing and EMR integrations. Of these patients, 700 were identified for review by Tempus staff and 16 consented to ELAINE 2 (Table 1).

Duration for full CTA execution for Traditional sites averaged 200.5 days (range, 142-257) and for TIME Trial sites averaged 7.6 days (range, 2-14). IRB approval time average for Traditional sites was 27.5 days (range, 12-71) and for TIME Trial sites was 3.0 days (range, 1-12 days). Duration from study activation to first consent was 33.3 days (range, 18-58) for Traditional sites and 8.8 days (range, 1-35) for TIME Trial sites (Fig 3). When a TIME Trial site was ready to open ELAINE 2, they sent an activation request to Tempus. The duration of this activation request to greenlight letter (ie, all tasks were completed and the patient was able to consent) averaged 14.2 days, with a range from 7 to 21 days (Fig 4).

Enrollment from start to finish lasted for a period of about 8 months in 2020 and 2021. The first patient enrolled was at a TIME Trial site 115 days before a Traditional site enrolled a patient. A total of five TIME Trial sites enrolled the first seven patients in the study. The largest enrolling sites were MD Anderson Cancer Center (five) and the Cleveland Clinic (four), both Traditional sites. The remaining Traditional and TIME Trial locations enrolled one to two subjects each (Fig 5).

A total of 39 patients consented (Traditional 23 and TIME Trial 16 patients) to the ELAINE 2 study. The Traditional sites enrolled 16 patients and the TIME Trial sites enrolled 13. Of the 29 patients enrolled, 25 were White, two were African American, and two subjects' race was not documented. Both African American patients were enrolled at Traditional sites. The trial completed enrollment in approximately 8 months, which was shorter than the anticipated enrollment duration of 12-18 months.

The TIME Trial sites had 158 total deviations for an average of 11.78 deviations per patient who consented. TIME sites also had a total of 173 adverse events with an average of 13.25 adverse events per patient enrolled. There were 7,140 total queries at TIME Trial sites for an average of 472.97 per patient enrolled. The Traditional sites had 104 total deviations for an average of 4.68 per patient who consented. Traditional sites also had a total of 316 adverse events with an average of 18.25 adverse events per patient enrolled. There were 9,269 total queries at Traditional sites for an average of 398.76 consented.

DISCUSSION

These data describe the operational metrics for enrollment of ELAINE 2, a phase II study in patients with advanced or metastatic hormone receptor–positive breast cancer requiring an *ESR1* mutation for enrollment. The clinical outcomes data for ELAINE 2 have been presented.[14] This study used both a Traditional method utilizing large academic medical centers, and community sites that participated in a JIT model. There were significant differences in the clinical oncology practices; for instance, Yuma Regional Medical Center employed five oncologists compared with MD Anderson Cancer Center, which has over 100 oncologists in a major urban setting.

FIG 2. Participating TIME Trial and Traditional sites.

Opening a clinical site using a JIT methodology is not a new concept and has previously included both community sites and large academic programs. Prior and ongoing JIT models include those from cooperative groups as well as industry sponsors. The novelty of the TIME Trial network, however, is the ability of the EMR integration to enable the rapid screening of thousands of patients leading to discrete patient identification on the basis of specific eligibility criteria.

TABLE 1. TIME Trial Site Patient Screening and Site Activation Data

Patients	No.
Screened (automated)	52,860
Reviewed by Tempus staff (manual)	700
Consented	16

There are several limitations to the data being presented. These include a lack of data regarding the total number of patients prescreened at Traditional sites for ELAINE 2. This information was not collected from Traditional sites because of prohibitions on patient data sharing before the patient signing consent and the increased burden on Traditional sites to collect these data. Other missing data include reasons for which the majority of the 700 patients (identified for TIME Trial Tempus staff to review) did not consent to the study. Although the exact numbers are not available, the most common reasons for not being eligible include the patient being deceased, declining patient performance status, exclusionary prior therapy, and too many lines of prior therapy.

There was a significant difference in the time to trial activation and IRB approval comparing Traditional with TIME

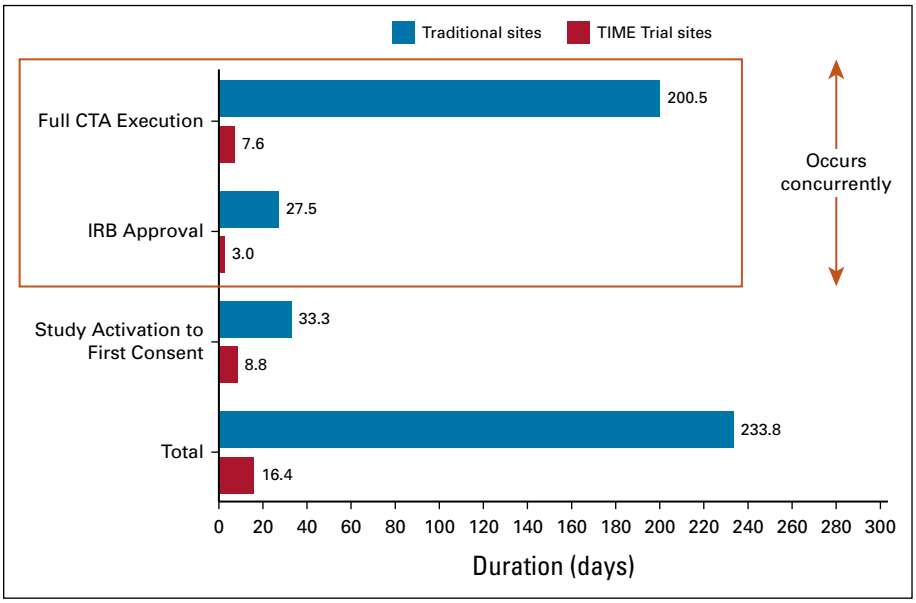

FIG 3. Site activation timeline to first consent. A comparison of the time duration from study activation to first consent in both Traditional and TIME Trial sites. CTA, clinical trial agreement; IRB, institutional review board.

Trial sites. Traditional sites took an average of 8 months for the completion of these tasks versus just over 2 weeks taken by TIME Trial sites. This difference in trial activations was predominantly from the TIME Trial sites using a standard template clinical trials agreement, regulatory documents, rate card, and a central IRB.

The number of patients who consented and failed the screening was higher for Traditional sites (seven) compared with TIME Trial sites (three). The TIME Trial sites opened approximately 4 months earlier than Traditional sites and enrolled the first seven patients. Both TIME Trial and Traditional sites contributed a significant number of patients. Except for the high performance of Cleveland Clinic and MD Anderson Cancer Center, there were no significant differences in patient recruitment in the remaining TIME Trial and Traditional sites. To optimize patient enrollment, future studies will likely need a mix of both larger Traditional sites and JIT community-based programs.

TIME Trial sites took approximately 9 days to consent a patient after trial activation compared with over 33 days for Traditional sites. This discrepancy is due to TIME Trial sites rapidly opening ELAINE 2 only when a patient was ready to

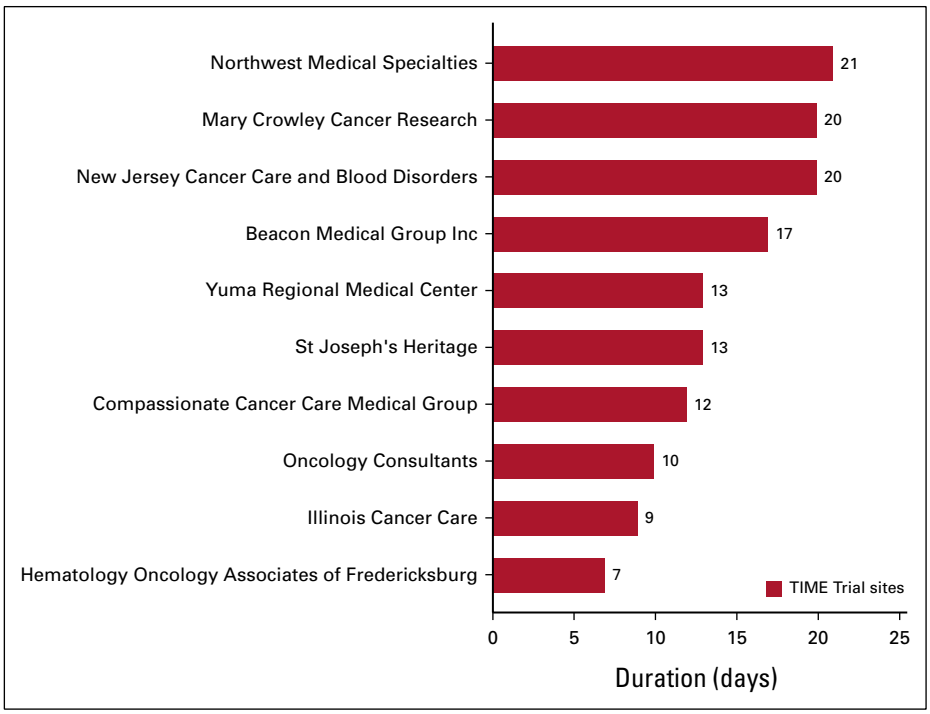

FIG 4. Activation request to greenlight letter. Duration from activation request to greenlight letter for each participating TIME Trial site.

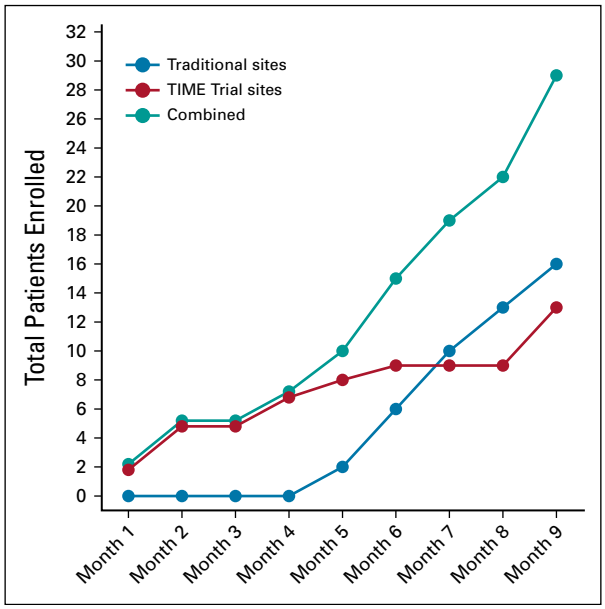

FIG 5. The ELAINE 2 study total patient enrollment. Total patient enrollment—graph representing the patients enrolled in Traditional sites, TIME Trial sites, and in total.

consent, compared with the Traditional sites activating the study before a specific patient is ready to enroll. This allowed TIME Trial sites to energize their research staff's efforts knowing that a patient was waiting to consent once the study was available.

Since there were only 39 patients who consented, it is difficult to determine if there were meaningful variances in data quality between the TIME Trial and Traditional sites. TIME Trial sites had more deviations and queries per patient screened than Traditional sites. Also, Traditional sites reported more adverse events per patient enrolled compared with TIME Trial sites. Although the medical research team responsible for study execution did not report an overall difference in the data quality, future studies of this combined approach should track closely each site's performance metrics.

Although the combination of using Traditional and TIME Trial sites decreased ELAINE 2 enrollment times by approximately 4-10 months, there are still many opportunities to improve. Increasing the number of EMR-connected institutions to JIT trial programs will improve the number of patients continuously screened for clinical trials. Advancements with NLP will allow for higher-fidelity automated patient matches, which will result in less burden on the site staff eligibility review. Although TIME Trial sites averaged approximately 14 days to active ELAINE 2, this process can continuously be improved. Finally, enabling larger academic medical centers to effectively participate in a JIT model has the potential to significantly increase patient enrollment and last patient in metrics.

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