Title: PD-1 SAIF: **P**romoting **D**evelopment of **One** **S**tandardized **A**lgorithm in **I**mmuno-Oncology at **F**ox Chase Cancer Center

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Abstract: The goal of this project is to install a unified, centralized, and standardized Immuno-Oncology (IO) Program that is agnostic to disease site and drug type and provides an educational foundation and institutional framework to all medical providers who interact with patients, all towards the ultimate goal of optimizing patient safety and minimizing morbidity from treatment-related immune-related adverse events (TR-irAEs) in patients receiving immunotherapeutic agents. The plan is split into three phases, with each phase focusing on a different aspect of education (patient-centered, internally-centered, externally-centered) to expand the understanding and recognition of TR-irAEs amongst patients and providers in a coordinated process. Each phase will build on the prior phase, making it expandable to provide education to local and regional primary care centers, and portable to enable installation at other tertiary and comprehensive cancer centers. Clinical and educational metrics are embedded to track and evaluate outcomes, and the program incorporates novel components to increase patient access to information and to their providers.

Keywords:
Treatment-related immune related adverse events
Immunotherapy
Patient-initiated contacts
Patient-centered education
Interactive on-line learning tool
Patient-reported outcomes

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I. **Overall Goal**

The overall goal of this program is to install a unified, centralized, and standardized Immuno-Oncology (IO) Program at Fox Chase Cancer Center (FCCC) that is agnostic to disease site and drug type and provides an educational foundation and institutional framework to all medical providers who interact with patients, all towards the ultimate goal of optimizing patient safety and minimizing morbidity from treatment-related immune-related adverse events (TR-irAEs) in patients receiving immunotherapeutic agents. With the expansion of immunotherapy agents in oncology, a knowledge gap has developed between medical oncologists who have learned how to safely administer these therapies by monitoring and treating emergent TR-irAEs, and other medical providers both in the oncology community (surgical and radiation oncologists, nurses, advanced practice clinicians [APCs]) and in the surrounding community. This program attempts to directly address this gap by providing education at knowledge-appropriate levels to patients and providers alike in a systematic fashion in order to improve outcomes. Once this program is established and validated, it will be <u>expandable</u> to provide education to local and regional primary care centers with which we share patients, and <u>portable</u> to enable installation at other tertiary and comprehensive cancer centers.

II. **Objectives**

A. Creation of a standardized, institutionally-designed set of information tools provided to all patients receiving treatment with an immunotherapeutic agent that is simple for patients to comprehend, provides meaningful information to providers outside of the institution, and can be accessed in a variety of formats depending on patient preference, all to decrease morbidity from TR-irAEs.

B. Development of provider-level specific educational seminars, tailored to each learning group, geared to enhance understanding and knowledge of IO therapies, and designed to positively impact patient outcomes based on provider-patient interactions in each unique setting.

C. Enriching the awareness and knowledge base of non-oncology providers at outside institutions in order to improve the prompt recognition of modern IO agents and their potential toxicities. This will be accomplished using live and/or on-line, case-based informational seminars directed at clinicians in primary care (PC) and emergency room (ER) settings.

III. **Assessment of Need**

A. <u>Overview</u>: The expansion of immunotherapy as standard systemic treatment in oncology, primarily with antibodies targeting immune checkpoints like programmed death 1 (PD-1), has resulted in increasing numbers of patients receiving anti-PD-1 (aPD-1) pathway targeting drugs. The side effects that occur with aPD-1 drugs differ from more well-recognized cancer treatments such as chemotherapy, as they occur mechanistically from a release on the usual innate immune system safeguards that protect against autoimmunity. This may result in incitement of an autoimmune attack (referred to herein as TR-irAEs) on any bodily organ that may require prompt initiation

of corticosteroids in order to reverse, but may easily be mistaken for a more typical chemotherapy-associated toxicity that could be treated supportively. With an expected serious TR-irAE incidence rate of about 15% based on clinical trial data, this means more TR-irAEs are occurring on an institutional level, as well as a national level when viewed from a public health perspective.[1, 2] Furthermore, given the relative novelty of these agents in the larger medical community, patients are more readily coming into contact with medical providers who have a limited knowledge and understanding of the toxicities associated with PD-1 inhibitors. At FCCC, a free-standing tertiary care cancer center and member of the National Comprehensive Cancer Network (NCCN) located in the densely populated southeastern Pennsylvania corridor, we receive referrals for all cancer types from a wide geographic area. This means our patients commonly receive their cancer care from FCCC, but depend on community hospitals in their neighborhood to provide on-going primary, urgent, and emergent care. This intersection of cutting edge cancer therapy that can result in unique and unpredictable toxicity, superimposed on a model where community-based care providers are often the first responders for acute issues but may not be educated on the nuances of immunotherapy management, has created a clinical care gap that is adversely affecting patient care and outcomes. This need has been recognized by oncology organizations, which have begun to publish guidelines to help standardize management.[3-7] Our program intends to close the gap on an institutional and locoregional level via standardized and innovative patient education tools and education programs targeted to providers (both at FCCC and at outside institutions) who interface with affected patients.

B. FCCC Assessment: Data generated from a chart review of 150 consecutive non-melanoma patients treated with aPD-1 immune checkpoint blockade (ICB) at FCCC demonstrated TR-irAEs in 41% of patients, with steroids required for treatment in 23%.[8] This is higher than published trials would predict, despite the fact that FCCC is an experienced academic cancer center that has been using aPD-1 agents since early phase I trials. We suspect this discrepancy is in part due to the extensive oversight and patient selection inherent in clinical trials, and that the "real-world" incidence of TR-irAEs will prove to be closer to our experience.[9-11] Since many TR-irAEs associated with ICB drugs can be treated and reversed if appropriately recognized, patient awareness and provider vigilance are paramount to ensuring the majority of patients will be evaluated in a timely fashion.

1. Patient-Centered Care- At FCCC, we have created a FCCC Immunotherapy Working Group (IWG) consisting of physicians, APCs, nurses, pharmacists, and information technology staff to improve outcomes in our patients being treated with aPD-1 agents. The first determination was that although all patients being initiated on aPD-1 therapy were receiving a FCCC-approved listing of potential side effects, no standardized protocol existed to inform patients when to call for potential symptoms, through what pathway to route them for evaluation, and what to do if presenting at an outside facility with a possible side effect. Best practices differed based on provider and disease group. The FCCC IWG determined that institutional informational materials and guidelines applied across disease types in a drug agnostic fashion would help ensure that all

patients would receive similar instructions.

2. Provider Education-The FCCC IWG also recognized that knowledge of aPD-1 drugs and recognition of potential TR-irAEs was variable across provider level and disease site group. While informational sessions geared towards non-physicians had been offered, no formal program focused on toxicity and structured based on education-level and provider-patient interaction was available. Thus, a second priority identified was the creation of a malleable education program run by medical oncologists but able to be adapted based on needs of the target audience (clinic nurses, infusion room nurses, APCs, etc.).

3. Locoregional Education- A major concern expressed by the FCCC IWG was the perceived lack of awareness of IO agents by local emergency room and primary care physicians. At least one publication has addressed the challenges facing community centers adopting pathways for these new therapies, but widespread systems-based practices have been lacking.[12] On a monthly basis, the FCCC morbidity and mortality conferences were being populated by cases of delayed diagnoses of TR-irAEs related to PD-1 inhibitors when patients first reported to providers outside our system. Despite the massive interest and surge of publications and education in the oncology community, awareness in the emergency medicine community, for example, seemed to lag behind IO prevalence. Case in point: a search of three of the most widely read, peer-reviewed emergency medicine journals, using the search terms “nivolumab” or “pembrolizumab” (the two most utilized PD-1 inhibitors) yielded only 2 citations, both of which were case reports of rare, single patient toxicities (search personally performed July 2, 2017). Consequently, the third focus of the FCCC IWG has been to harness the experience and knowledge gained at FCCC regarding the use of aPD-1 agents and impart the necessary information to primary care and emergency medicine colleagues at neighboring facilities.

IV. Target Audience

A. The target audience of this initiative is three-fold and highly dependent on the objectives and phased design discussed in the next section. FCCC as an institution, with its long-established mission towards excellence in patient care, education, and research, is fully invested in the success of this initiative, underscoring the commitment of all involved parties. Upon full implementation, we anticipate this phased-design will provide a framework to transport our program to other cancer centers.

1. Patients being treated with ICB- All patients at FCCC who are to receive treatment with aPD-1 ICB will receive specific, standardized education materials prepared at FCCC to optimize understanding of TR-irAEs. This information will be available in a variety of formats based on each individuals’ needs and preferences.

2. FCCC physicians in departments outside of medical oncology and non-physician staff members- Education will be provided to FCCC faculty physicians in surgical oncology, radiation oncology, and internal medicine, individually highlighting topics directly applicable to their specialties and interactions with

patients. We also intend to provide tailored education to nurses in various capacities at FCCC (clinic, infusion room, phone triage), pharmacy, and APCs.

3. Non-oncology physicians at local medical centers- Educational programs for continuing medical education (CME) credits will be prepared and offered to local physicians in the emergency medicine and primary care settings to expand their awareness and knowledge of IO agents for oncology. These will initially be offered to hospitals in our immediate area, but will be expanded as time and resources allow.

V. Project Design and Methods

A. Overview: The project will be divided into three phases and is illustrated in Figure 1. While the phases will be carried out consecutively, the planning for each may occur concurrently and outcomes from each phase will impact the planning and execution of subsequent phases. The project will be coordinated by the FCCC IWG described above. The overall strategy is to implement education across the institution in a phased approach in order to optimize utilization and clinical outcomes, starting with direct patient education, followed by a widening informational catchment focusing on institutional staff, and finally with clinicians at outside institutions.

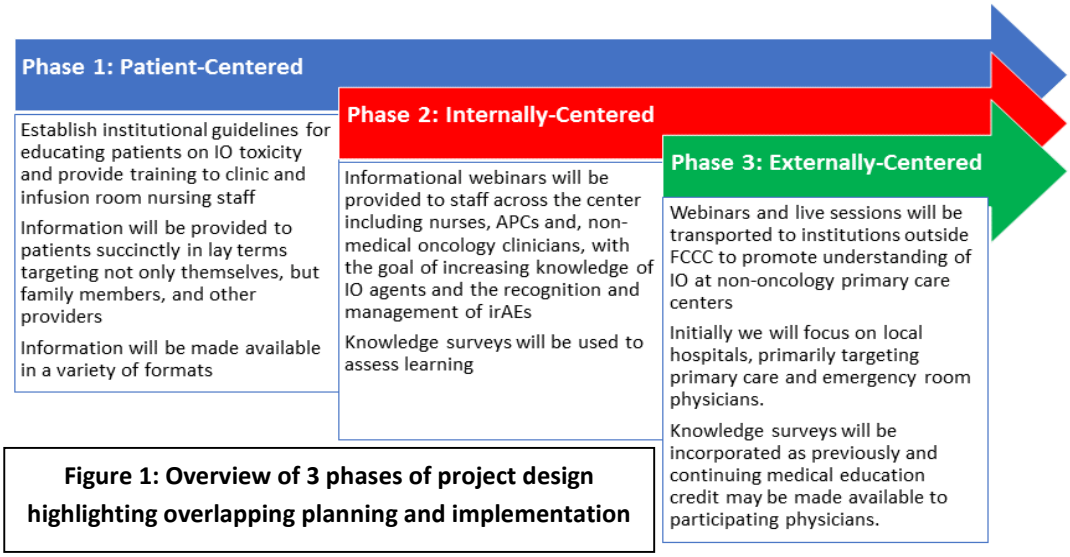

Figure 1: Overview of 3 phases of project design highlighting overlapping planning and implementation

B. Phase One- Patient-Centered Education: This phase will focus on providing clear and simple information on TR-irAEs directly to patients in a variety of formats. The goals of the flow of information will be to impart lay instructions integral to promoting patient understanding of the risks of IO therapies and allowing patients to easily disseminate that information to other healthcare providers with which they interact. Content will be evidence-based, prepared and vetted by the FCCC IWG, and regularly reviewed and updated. Information will be made available in several formats, allowing patients to choose the format(s) in the ways in which they prefer to receive important educational information.

1. *Print*- FCCC has a standard institutional consent form and policy

applicable to all patients receiving anticancer therapy. This is generally a list of potential side effects listed in groups and separated by likelihood of attribution, and this will be provided to all patients.

2. *Information card*- All patients will be offered a wallet-sized information card designed to be given to providers outside of FCCC to alert them that the patient is receiving aPD-1 therapy. Patients will be instructed to display this card anytime they are evaluated by another clinician or if there is a concern about a new sign or symptom that could be related to treatment. A prototype created by the FCCC IWG is shown in Figure 2.

3. *Wearable*- Patients will be offered a bracelet, designed and created by the FCCC IWG, that identifes them as receiving an IO agent and directs them to call the 24-hour FCCC number for and questions, concerns, or if patient is found in a state unable to provide that information.

4. *Interactive On-Line Learning Access*- Once consented to start treatment

Figure 2: Prototype patient information card

with an aPD-1 drug, patients would be offered access to an on-line learning tool embedded in our institutional patient-specific web-based program known as MyFoxChase. The MyFoxChase account is an easy-to-use website available to all patients who choose to sign up and allows patients to track and manage their schedules, check test results, and contact their clinicians. In collaboration with the MyFoxChase team, functionality exists to create a specific link for each patient on their own personalized website. This link would only be visible to patients once they have agreed to sign informed consent to start aPD-1 treatment and would provide access to a variety of resources that may benefit the patient. Some content would be created and approved by the FCCC IWG, but links to approved external sites would also be made available. Examples of resources that would be available to patients via this site includes: links for patients to seek more information about the drug they are receiving, functionality to print or electronically share drug-specific information with other people, direct access to contact their clinician and treatment team via our secure messaging system, and the capability for patients to report their symptoms. Web-based patient reported outcomes (PROs) in oncology patients on

chemotherapy have recently been shown to improve overall survival, in addition to multiple quality of life measures.[13] We hypothesize this capability would increase patient reporting of symptoms, potentially leading to improved recognition of early TR-irAEs and ultimately improved outcomes. To our knowledge, this would be the first pilot evaluation of PROs for patients on IO agents.

The first step in this phase will be training of all medical oncology clinic nurses and infusion room nurses to ensure standard dissemination of general information and the wallet cards to all patients receiving ICB agents. Once made available, all patients receiving an aPD-1 drug will be given a wallet card by their clinic or infusion room nurse. All patients, including those already receiving an ICB agent prior to roll-out of the wallet cards, will be offered the card by the infusion room nurse administering the medication. Receipt of the card (or patient refusal) will be documented by the nurse in a searchable electronic medical record (EMR). The same system will be put in place for the wearable device. Patients will also be given instructions about setting up their MyFoxChase account and then will be provided access to the aPD-1 specific content. Initially, this will be introduced as a pilot program in the genitourinary (GU) group where all patients receiving aPD-1 drugs will be asked if interested in receiving all above interventions and consented to participate. As described below, we will then track various metrics in this group including website utilization, patient-initiated contacts (PICs), and clinical outcomes to assess feasibility and measure the impact of these interventions. Once feasibility and benefit is assessed and the program is optimized, it would be rolled out institution-wide and patients would be able to choose the resources most applicable to them.

C. Phase Two- Internally-Centered Education: The focus of phase two will be on educating FCCC staff including clinic/phone triage/infusion room nurses, APCs, pharmacists, and non-medical oncology clinicians (internal medicine, surgical and radiation oncology). Live educational seminars conducted by medical oncologists and tailored to each target group will focus on an overview of aPD-1 drugs and how to recognize and treat potential TR-irAEs. Seminars will be recorded and made available as a webinar to allow staff to view at a convenient time if unable to make live sessions. Knowledge surveys administered before and after the program will be utilized to track effectiveness and improve the program for phase three.

D. Phase Three- Externally-Centered Education: The experience garnered from the first two phases will be adapted in phase three to conduct educational seminars to institutions outside FCCC to promote understanding of relevant IO information geared to community primary, urgent, and emergency care physicians. This phase will be designed in collaboration with the FCCC Care Connect program (CCP), a home-grown collaboration between FCCC and community physicians designed to foster seamless patient flow and transfer of information between FCCC and its extended network of primary care doctors. The CCP has extensive experience organizing and conducting successful educational sessions for local doctors and is an eager and willing participant of the PD-1 SAIF initiative. CCP is described in further detail in the organizational details

section. Initially we will focus on local hospitals in our immediate catchment area, but the program could be easily structured to be applied to more distant centers. We plan to first work with Temple University Hospital (TUH) and Jeanes Hospital (JH), two hospitals with which we have a direct relationship. TUH is a large university hospital in an underserved neighborhood that is affiliated with FCCC, while JH a community hospital that is part of the Temple-FCCC system and resides on the same campus as FCCC. These varied centers with which we already have an intimate working relationship would provide an ideal initial experience to plan and validate our educational programs. Subsequently, we plan to include at least 6-8 institutions in year two of the project, with more included as time and resources allow. Continuing medical education credits will be made available to physicians who participate in order to enhance attendance. In time, the program may also be expanded to provide nursing and APC education to outside institutions as well.

VI. Evaluation Design

A. Overview: Each phase will incorporate metrics to measure effectiveness and quality improvement (QI) and these are outlined in table 1. Assessments of clinical outcomes will be paramount, but evaluations of QI pertaining to installed interventions and knowledge uptake will also be analyzed. We plan to present our results at national meetings and publish in a peer-reviewed journal, and if successful, would offer guidance and oversight in implementing similar programs at other comprehensive cancer centers, with all educational materials made available to other centers as needed.

Phase	Outcome Measure	Method of Assessment	Goal
1	Proportion of patients given appropriate educational materials	Assessed in infusion room at 1st IO drug administration and tracked via EMR	>95% of patients receive appropriate materials
1	Percentage of PICs compared to institutional norm	Manual monitoring of volume of PICs	20% increase in PICs
1	Percentage of patients referred for urgent evaluation or admitted for work-up of possible TR-irAEs	Manual monitoring of patient referrals and admissions	10% increase in patients referrals or admissions
1	Percentage of patients who require oral or IV steroids for management of a TR-irAE	Manual accounting of patients who receive oral or IV steroids for a TR-irAE	10% decrease in patients who require oral or IV steroids
2 & 3	Improvement in knowledge of IO learning objectives amongst session attendees (FCCC staff, outside clinicians) in each target group	Pre and post seminar knowledge surveys	50% improvement in each target population on the post-seminar assessment survey

Table 1: Metrics evaluated to assess benefit of PD-1 SAIF Program
IO: Immuno-Oncology, EMR: Electronic medical record, PIC: Patient-Initiated contact, TR-irAE: Treatment-related immune-related adverse event, IV: intravenous, FCCC: Fox Chase Cancer Center

B. Phase 1

1. *Pilot Program*- In order to assess feasibility and efficacy of the planned interventions in a controlled fashion prior to institution-wide roll out, we plan to institute a single disease-site pilot program. First, baseline values for planned metrics need to be evaluated at our center, and these will serve as comparators to the pilot interventions. Baseline data on patient outcomes will be measured

during a 4 month run-in period conducted with patients receiving standard of care aPD-1 drugs (conducted concurrently with development of the educational intervention). Metrics will include number of patient-initiated contacts (PICs, defined as phone calls or emails received by our in-house nurse-driven phone triage), admissions to our direct referral unit (DRU, in-house urgent care clinic), emergency room (ER) visits, hospital admissions and need for systemic steroids for a suspected TR-irAE. Data will be tabulated by the program project manager (PM), and once baseline values established, an FCCC-wide, protocol-driven program will begin.

2. *FCCC multi-disease program*: An institutional review board (IRB) approved protocol will be required and obtained, and all patients entering the pilot program will give written informed consent to participate and have this data recorded and tracked. During the pilot, all participating patients will be monitored for the aforementioned metrics and evaluated as below. Patients will be accrued across the center over one year, but outcomes will be monitored for only 3 months of therapy.

a) PICs: We anticipate approximately 50 patients will be tracked during the run-in, and 200 patients will be evaluated after the educational intervention is in place. If the populations change over time, we will adjust for those factors in all subsequent tests (via multivariate regression models). The volume of PICs will be compared over the 1st 3 months of therapy, using Poisson models with an offset for length of immunotherapy treatment (to account for patients who stop therapy before 3 months). If the average number of PICs per patient per month in the baseline phase is 2, we will have 80% power with 5% 2-sided type-I error to detect a rate of 2.4 PICs per month in the intervention phase.

b) Other clinical metrics: We will also compare how often these patients present to our DRU, an ER, how many get admitted for a possible TR-irAE, and how many receive steroids. Results of these metrics will be compared to the baseline levels obtained and evaluated as secondary endpoints. We anticipate these interventions will result in an increased number of patients being referred for evaluation to the DRU or an ER, but a decrease in the proportion of patients who require systemic steroids. We will also compare to our previously reported FCCC experience.[8]

c) Information card: We will evaluate the effectiveness of this intervention by measuring uptake. Nursing will document in the EMR when a card is given (or refused) using a searchable electronic smart-phrase. By calculating the number of patients with this smart phrase over the total number of unique patients receiving the IO agents of interest in a defined time period, we will be able to measure the uptake. This may also be utilized for the wearable bracelet. The goal will be > 95%.

d) *Interactive On-Line Learning Tool-* Patients will be given instructions on how to set-up their MyFoxChase account. The MyFoxChase program allows for the ability to track how often patients access the site and what content

and links receive the most clicks. This information will be used for internal assessment in a de-identified fashion to enable improvement of the site over time, and will be measurable to enable reporting on site components most often accessed to help structure future sites at other centers.

e) *PRO System*: The PRO system will be monitored by the PM or an APC, with the information collected made available to the treating clinician. Patients who utilize the PRO system and not the messaging system, and vice versa, will be identified and compared for clinical outcomes and incidence if TR-irAEs. Clinical outcomes will be summarized, described, and analyzed using logistic regression models if appropriate (i.e. a sufficient number of events occur). We expect the on-line PRO system will also contribute to the expected 10% decrease in the need for systemic steroids for TR-irAEs. We acknowledge it will be difficult to differentiate the relative benefit and contribution of the PRO initiative versus the increased access to clinicians via the on-line messaging system when assessing changes in patient contacts and steroid usage. However, we expect both will be important to improving recognition and management of TR-iRAEs, thus the potential benefit outweighs the difficulty in assigning attribution.

C. Phase 2 and 3: During the information sessions in phase two and three, knowledge surveys will be administered before and after each seminar, graded, and compared to assess knowledge uptake. On-line webinars will include the same pre-test and post-test offered during the live talks. During phase two, staff who attend live sessions will be asked to fill out a second knowledge assessment at a later date to assess retention. Provider pre-post knowledge scores will be tested using paired t-tests or Wilcoxon signed-rank tests. Upon the roll-out of the education seminars at FCCC, we will continue to assess for patient outcomes as measured by incidence of TR-irAEs and need for systemic steroids.

VII. Work Plan and Deliverables Schedule

We anticipate completing phase one, with approval of the patient resources, completion of initial nursing education, and assessment of baseline metrics, within 8 months. The FCCC IWG is already working on obtaining approval of the information card format for patient utilization and will soon commence staff education to facilitate procedural understanding. Educational seminars to FCCC staff outlined in phase two would occur over a six month period, with the program content being created and finalized concurrently with phase one. Educational sessions to outside institutions would occur over a one year period, with plans for 6-8 sessions during that time frame. Analysis of outcomes tools would primarily occur during year 2. We expect to have data ready for presentation and publication in the second part of year 2 of the grant, which would be early to middle 2019. In total we expect the project would be completed within 2 years, but sustainable indefinitely. This is illustrated in table 2.

VIII. Conclusion

We believe this *PD-1 SAIF* project at FCCC represents a unique opportunity to install a

ground-up program focusing on patient and staff education to improve outcomes and morbidity around a rapidly emerging and expanding clinical need. We are not aware of any published materials outlining a similar coordinated approach being incorporated at any other cancer center, and we believe our size and experience with IO since inception creates an ideal environment for success. The incorporation of an interactive on-line application as part of the first phase of the project offers a novel and innovative component that we anticipate will enhance the patient experience, increase patient-provider communication, and improve symptom reporting. Finally, the design of the project allows for the potential to expand education to centers nationwide and to recreate a similar initiative at other cancer centers if proven successful.

Table 2: Expected Deliverables Timeline

Phase	Deliverable	Estimated Date(s)
1	Completion and approval of patient resources	October 1, 2017
1	Begin assessment of baseline metrics on pilot program	October 1, 2017
1	Complete assessment of baseline metrics on pilot program	February 1, 2018
1	Multi-site protocol written and moved through IRB approval	November 2017- January 2018
1	Begin accrual to multi-site program	February 1, 2018
1	Complete accrual to multi-site program	March 1, 2019
1	Evaluate and analyze collected data from multi-site program	March 1, 2019- June 2019
2	Writing and planning content and lecture slides for staff educational seminars	October- December 2017
2	FCCC staff seminars planned, scheduled and produced (2-4/month)	February 2018-August 2018
3	Scheduling and content prepared for educational seminars outside FCCC	June-August 2018
3	Live educational seminars offered to community physicians outside FCCC (estimate 1 every 6-8 weeks)	September 2018- August 2019
All	Prepare data for presentation and publication	January-June 2019

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