

## Research Letter

# Effectively Conducting Oncology Clinical Trials During the COVID-19 Pandemic



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## Abstract

**Purpose:** Clinical trial enrollment has declined globally as a result of the coronavirus disease 2019 (COVID-19) pandemic. This underscores the importance of structured methods to continue critical medical research safely and efficiently.

**Methods and Materials:** We report the effect of a phased trial reopening strategy, remote research staffing, and telemedicine on cancer trial enrollment at one of the largest radiation oncology academic cancer centers. In phase 1, trials investigating definitive therapeutic benefit were opened, followed by trials not increasing patient exposure or pulmonary toxicity risk in phase 2. During phase 2.5, multicenter trials reopened and limited research staff were allowed on site.

**Results:** Despite initial enrollment declines during the early pandemic, the percentage of new patients enrolling in clinical trials from March to August 2020 was 8.8%, and represented a 10.5% relative increase from 2019. Monthly accrual enrollment from March to August 2019 ranged from 42 to 71, compared with enrollment during COVID-19 from 23 to 73 patients ( $P < .001$ ).

**Conclusions:** Through a phased approach to trial reopening and adaptive techniques, the division of radiation oncology maintained cancer trial accrual during the COVID-19 pandemic. The experience may help centers maintain accrual, preserve clinical trial integrity, and minimize risk to patients and staff.

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## Introduction

In response to the coronavirus disease 2019 (COVID-19) pandemic, the U.S. Food and Drug Administration provided guidelines to safely and efficiently continue critical medical research.<sup>1</sup> It included nonbinding recommendations for resource allocation, remote monitoring and consenting, and new methods for clinical outcome assessments. At one of the world's largest cancer centers, the division of radiation oncology conducts over 100 clinical protocols. We analyzed how a phased approach to

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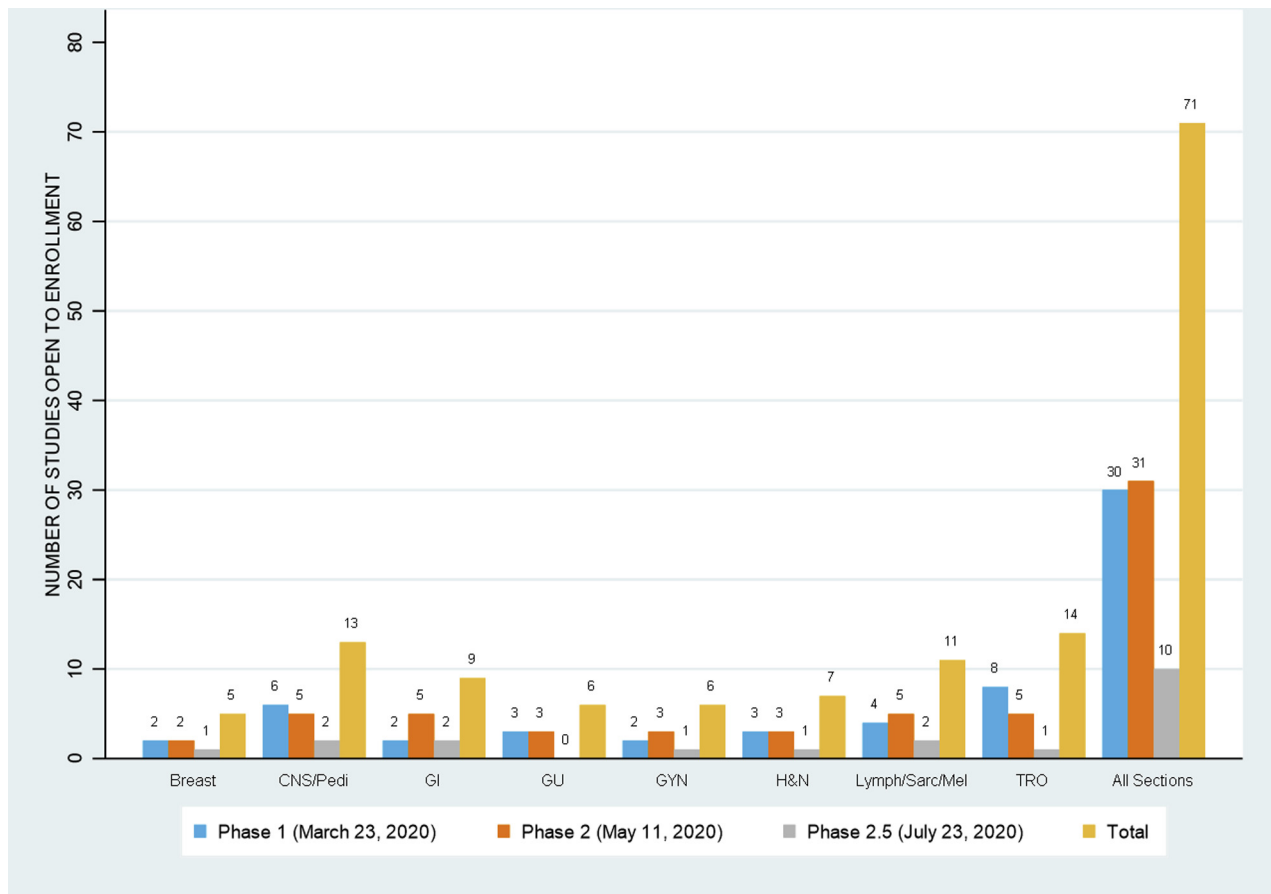
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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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**Figure 1** Number of therapeutic protocols opened in radiation oncology by disease site during phased reopening. *Abbreviations:* CNS/Pedi = central nervous system/pediatrics; GI = gastrointestinal; GU = genitourinary; GYN = gynecology; H&N = head and neck; Lymph/Sarc/Mel = lymphoma/sarcoma/melanoma; TRO = thoracic radiation oncology.

trial reopening, remote coordination of research staff, and telemedicine allowed for continuing cancer clinical trials.

## Methods and Materials


In March, we paused certain clinical trials, required research staff to work remotely, and planned a multiphase approach for reopening trials (Figs 1 and 2). We adopted institutional policies to mitigate the risk of COVID-19 exposure, including limiting laboratory and clinical personnel interaction. For phase 1, we selected therapeutic protocols that met specific criteria, such as potential for lifesaving, therapeutic, or clinical benefit while minimizing correlative procedures. We assessed if trials increased patient visits beyond standard-of-care or if investigational agents increased immunosuppression or pulmonary toxicity risks.

During phase 2 in May 2020, we considered reopening trials that would not increase blood transfusion or pulmonary toxicity risk, use of personal protective equipment, or on-site research personnel. Trials could include research biopsies if required for enrollment. Procedures to

pass research samples through a designated moat protected research staff from interaction with clinical teams.

In June, an intermediate phase 2.5 approach prioritized reopening cooperative group or national multi-investigator trials while allowing limited research staff on-site for critical functions such as biospecimen transport. Cross-coverage enabled research staff to assist with consent, specimen transportation, and measuring outcomes. With telemedicine, staff could help prepare remote consents and collect follow-up data. As patients minimized on-site follow-up visits, there was increased coordination across multiple departments to record patient adverse events, and trials allowed mail distribution of medications to assist with local administration of therapy. A planned phase 3 could include increasing on-site research staff to 25%, contingent on 2 weeks of decreasing community COVID-19 rates.

We compared enrollment during fiscal year 2020 (FY20) from September 2019 to August 2020 to fiscal year 2019 (FY19) from September 2018 to August 2019. Chi-square test was performed to evaluate the difference in number of patients (n) enrolled per month from March to August of FY19 compared with FY20. To account for

Phase	Effective March 19 <sup>th</sup> , 2020	
1	Radiation Oncology clinical research staff off-site – emphasis on remote working Minimal trials for new patient entry (approx. 1-10) per disease site section No clinical research biopsies Minimize correlative laboratory studies to those occurring with skeleton staff in the institutional clinical translation research or tissue banking centers	Can move back if signs of a second peak develop 
2	Effective May 11 <sup>th</sup> , 2020 (modified July 17 <sup>th</sup> , 2020) Limited increase of trials open to new patient entry Allow limited on-site research staff for critical functions Transport research samples through designated moat to avoid interaction between research and clinical staff Allow research biopsies if required for enrollment and/or participation Allow correlative laboratory studies that can be collected through research moat and transported in compliance with specimen guidelines Support COVID-19 related trials	
3	TBD: Pending decreasing infection rate in greater Houston for 2 weeks Increase trials approved with up to 25% rotating on-site research staff Prioritize trials supported by institutional strategic initiatives Increase clinical translation research or tissue banking centers to full staffing	
4	TBD: Pending institutional, Houston and State declarations Resume full clinical research activities with full lab and correlative support	

\*modified for Radiation Oncology Division Departments

**Figure 2** Institutional guidance for clinical research trial reopening.

changes in clinic volume between the 2 years, we calculated the percentage of patients enrolled as a fraction of the number of new patients treated in clinic. Lastly, the relative difference in the percent enrollment from fiscal year 2019 to 2020 was defined as the change in percent enrollment.

### Results

Forty-four, 139, and 73 patients enrolled in therapeutic trials during phase 1, phase 2, and phase 2.5, respectively, which corresponds to 1.2, 2.4, and 2.5 patients enrolled per day in each phase. Monthly accrual pre-COVID-19 from September 2019 to February 2020 ranged from 50 to 75 patients, in contrast to enrollment during COVID-19 after March 2020 ranging from 23 to 73 patients (Table 1, Fig 3). Enrollment from FY19 March to August ranged from 42 to 71, which is statistically different from the same months during the COVID-19 pandemic in FY20 ( $P < .001$ ). Enrollment as a percentage of patients treated in the department pre-pandemic in FY20 ranged from 7.9% to 10.6% before March, dropping to 4.9% in April 2020 and rebounding to 11.3% in July with increased telemedicine resources. When evaluating changes in enrollment between FY20 and FY19, there was a relative decrease of 37.6% (FY20  $n = 23$  of 469, 4.9% vs FY19  $n = 56$  of 712, 7.9%) and a decrease of 7.2% (FY20  $n =$

38 of 500, 7.6% vs FY19  $n = 58$  of 708, 8.2%) in April and May 2020, respectively. With increased telemedicine, enrollment relatively increased by 74.1% (FY20  $n = 63$  of 585, 10.8% vs FY19  $n = 42$  of 679, 6.2%) and 45.7% (FY20  $n = 73$  of 647, 11.3% vs FY19  $n = 55$  of 710, 7.7%) in June and July 2020 compared with 2019. Overall, the 6-month percent enrollment during COVID-19 was 8.8%, reflecting a relative increase of 10.5% from FY19 to FY20. The pandemic also affected our geographic catchment area for radiation oncology patient enrollment across the institution, with a greater proportion of enrollees living in Texas in FY20 (Table 2).

### Discussion

Modeling institutional guidance, our division instituted a phased approach to maintain trial accrual by first prioritizing therapeutic trials with potential clinical benefit over standard-of-care. It was followed by reopening trials that could be conducted safely with minimal operational logistics. Adaptive techniques in remote staffing and telemedicine resulted in enrollment being maintained at 8.8% during the first 6 months of the pandemic and a notable 10.5% gain from the prior year. It is in contrast to a national 62% enrollment decrease in the United States in March 2020 compared with 2019 by Medidata.<sup>2</sup> In an update, the United States' percent change in 2020 versus

**Table 1** Number and percentage difference of patients enrolled on radiation oncology clinical trials in FY20 compared with FY19

	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	6-Months average*	Yearly average
FY19	63	45	55	57	70	56	59	56	58	42	55	71	56.8	57.3
FY19 NPT	679	712	613	598	755	698	718	712	708	679	710	694	703.5	689.7
% Enrollment <sup>†</sup> FY19	9.3%	6.3%	9.0%	9.5%	9.3%	8.0%	8.2%	7.9%	8.2%	6.2%	7.7%	10.2%	8.1%	8.3%
FY20	64	64	64	50	75	72	66	23	38	63	73	48	51.8	58.3
FY20 NPT	636	768	612	633	787	682	761	469	500	585	647	568	588.3	637.3
% Enrollment FY20	10.1%	8.3%	10.5%	7.9%	9.5%	10.6%	8.7%	4.9%	7.6%	10.8%	11.3%	8.5%	8.8%	9.1%
% Change in % enrollment <sup>‡</sup>	8.5%	31.9%	16.6%	-17.1%	2.8%	31.6%	5.5%	-37.6%	-7.2%	74.1%	45.7%	-17.4%	10.5%	11.4%

Abbreviations: COVID-19 = coronavirus disease 2019; FY19 = fiscal year 2019; FY20 = fiscal year 2020; NPT = number of patients treated.

\* Six months average is the most recent 6 months (Mar to Aug).

<sup>†</sup> Percent enrollment refers to the percentage of patients enrolled in clinical trials in relation to the total new patients treated in the division.

<sup>‡</sup> Percent change in percentage enrollment refers to the percent difference in percent enrollment between FY20 and FY19 and accounts for changes in clinic patient volume.

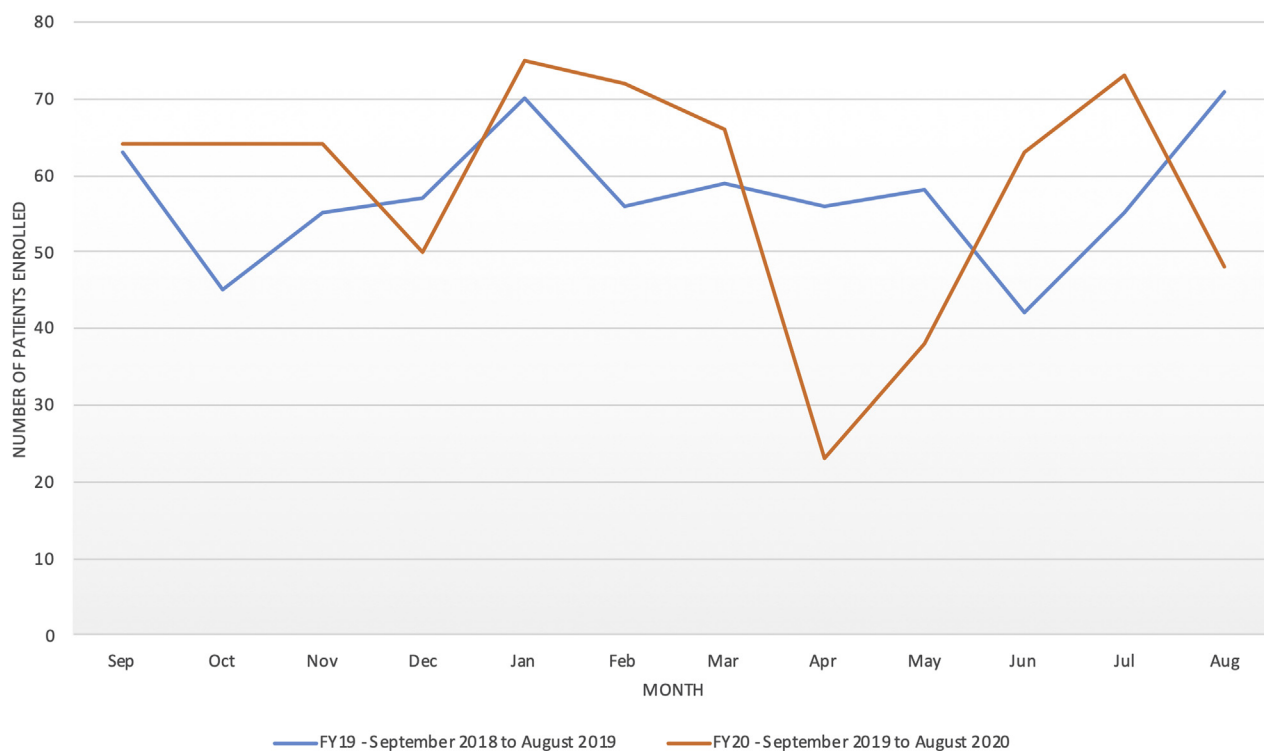
2019 was -31% in June, -14% in July, and -22% in August.<sup>3</sup>

Regulatory bodies have issued nonbinding recommendations on methods to adjust for changes in the pandemic, including remote consenting or research evaluations. At our institution, remote consenting was first integrated in clinics and later in research. It enabled us to mitigate initial decreases in enrollment. Remote digital data collection and telemedicine may increase trial screening, the speed of remotely reporting adverse events or follow-up data, and potentially allow for advanced analytics with machine learning to detect proximal outcomes.<sup>4,5</sup> Moreover, because poor accrual accounts for 43% of early-terminated phase II-III trials,<sup>6</sup> virtual clinical consultations for patients eligible for trials provide an opportunity to increase enrollment and patient satisfaction due to convenience.<sup>7</sup> Thus, it may further mitigate enrollment challenges and help reach wider populations during the COVID-19 pandemic.<sup>8</sup>

Similar to our approach, the U.S. Food and Drug Administration offered recommendations on prioritizing trials appearing to offer clinical benefit. Clinical Trials Transformation Initiative also published best practice guidelines.<sup>9</sup> Institutional review board communications included reducing study visit frequency, converting to telemedicine, and allowing for telephone assessments, off-site labs, or alternative drug delivery similar to other institutions.<sup>10</sup> Early in the pandemic, potential issues facing clinical trials led to a call to maintain clinical trial integrity by delaying or phasing enrollment, maintaining connections with participants, documenting the effect of COVID-19 on trials, and revising statistical methods if needed.<sup>11,12</sup> Other approaches suggested stratifying patients by degree of risk, especially if older or with comorbidities, which reflect some of our strategies.<sup>13,14</sup>

With only 8% of all patients with cancer enrolling in clinical trials,<sup>5</sup> more virtual trials could improve enrollment while also potentially shifting geographic demographics as seen at our center. As we moved toward regional marketing during the pandemic, we saw increases in percentages of in-state participants. In a survey of U.S. Cancer Centers of Excellence with above-average recruitment of ethnic minority groups, such as our center, it was determined that increasing local community engagement through strategic initiatives could be an important component for increasing diversity with virtual trials in the future.<sup>15</sup>

Observation data have limitations, and there may be unmeasured confounding factors contributing to enrollment patterns during COVID-19. For instance, several institutional policies and changes in clinic procedures were necessary to adjust to the pandemic. However, we took into account how relative changes in clinic volume could affect enrollment.



**Figure 3** Enrollment by month in fiscal year 2020 (FY20) compared with fiscal year 2019 (FY19).

**Table 2** Trial enrollment geographic catchment by state from 2019 to 2020

Fiscal year	State	No. of enrollments*	Enrollments (%) <sup>*†</sup>	Fiscal year	State	No. of enrollments <sup>*†</sup>	Enrollments (%) <sup>*†</sup>
FY19	Texas	630	66.3%	FY20	Texas	729	72.6%
FY19	Louisiana	80	8.4%	FY20	Louisiana	65	6.5%
FY19	Florida	27	2.8%	FY20	Mississippi	32	3.2%
FY19	Mississippi	23	2.4%	FY20	Florida	20	2.0%
FY19	Arkansas	17	1.8%	FY20	Alabama	18	1.8%

\* This number reflects unique patient enrollments of radiation oncology patients who were enrolled in institution-wide trials.

† Percentages do not sum to 100% as these represent enrollment numbers for the most highly represented states.

### Conclusions

Our departments were able to increase clinical trial enrollment with a detailed stepwise approach that prioritized patient safety and telemedicine techniques. Using techniques to preserve integrity of oncology trials in the COVID-19 era offers hope for patients with cancer while advancing academic science.

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