

# Impact of the COVID-19 Pandemic Mitigation Strategies on Cancer Clinical Trials

*Preliminary Findings of a Friends of Cancer Research–American Society of Clinical Oncology Study*

**Friends of Cancer Research Annual Meeting 2022**

## Background

Enrollment in clinical trials is key to advancing new treatments for patients with cancer. At the beginning of the COVID-19 pandemic, patient enrollment and treatment in cancer clinical trials were negatively impacted, in large part due to approaches to adapting to the COVID-19 pandemic public health emergency, including social distancing and lockdowns. Recognizing the challenges of recruiting and treating patients in clinical trials during the pandemic, researchers, regulators, and policymakers moved rapidly to support modifications to traditional clinical trial processes to enable important research and care to continue, both for ongoing trials and those initiated during the pandemic.<sup>1</sup>

Anecdotally, many researchers have proposed that retaining these modifications in future trials could reduce inefficiencies and burdens, thereby increasing patient access to clinical trials. However, there is a knowledge gap in the published literature about how sponsors and sites adjusted clinical trial practices during the COVID-19 pandemic and what impact these changes had on the quality of trial data and patient access. To address this, Friends of Cancer Research (*Friends*) and the American Society of Clinical Oncology (ASCO) partnered to evaluate how the modifications to trial conduct adopted during the pandemic affected the conduct of clinical trials. If the impact of these changes, especially on data quality, has been sufficiently minimal, then maintaining these beneficial flexibilities could lead to increased patient access to future clinical trials and could speed the conduct of trials, thus accelerating new treatment discovery. Further, there may be an opportunity to streamline clinical trial operations by employing common reporting and documentation requirements for certain modifications, including protocol deviations (PDs) and amendments, as recommended by ASCO in its 2021 report, American Society of Clinical Oncology (ASCO) Road to Recovery Report: Learning from the COVID-19 Experience to Improve Clinical Research and Cancer Care.<sup>2</sup>

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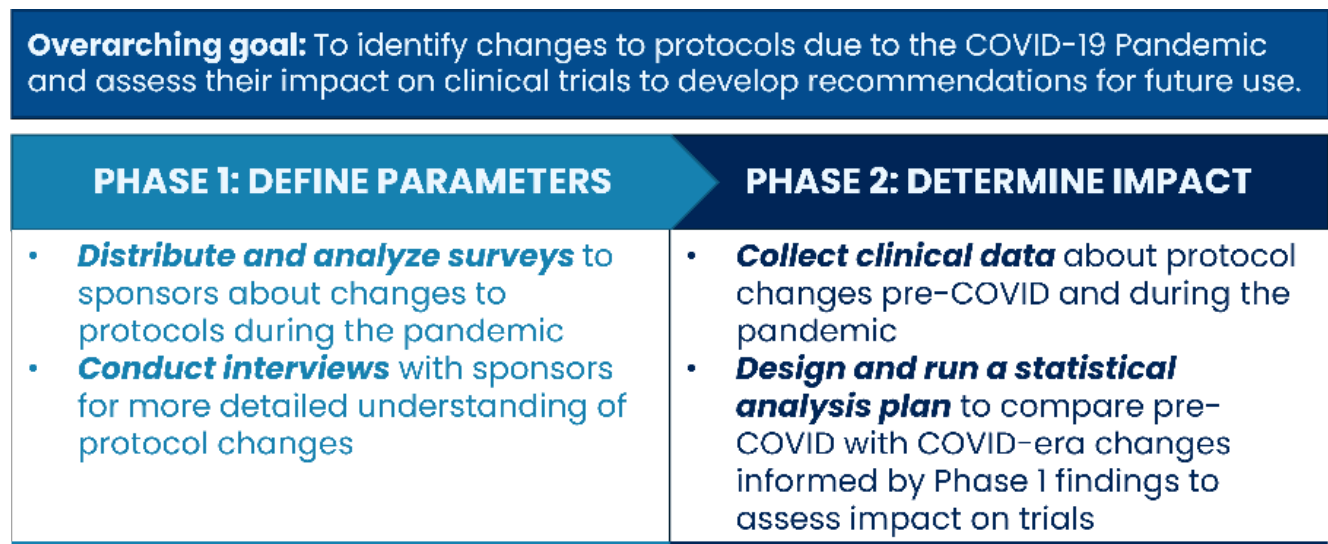
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## Approach

ASCO and *Friends* partnered with two academic co-chairs to establish a steering committee who worked closely with a multi-stakeholder task force comprised of representatives from academic and community oncology practices (including clinical investigators and research staff), patient advocate groups, the U.S. Food and Drug Administration (FDA), the National Cancer Institute (NCI), pharmaceutical companies, a contract research organization (CRO), and ASCO and *Friends* staff. At the outset, the primary objectives of the Task Force were, 1) to assess potential changes to data quality, as reflected by changes in patterns of PDs during the COVID-19 pandemic; 2) to describe mitigation strategies that were employed to reduce PDs; and 3) to determine the broader impact of the mitigation strategies on the conduct of clinical trials. If the mitigation strategies adopted during the pandemic result in sufficiently minimal adverse consequences to data quality and trial conduct, we will formulate recommendations to retain the changes going forward.

To accomplish the research objectives, the Task Force is implementing a multi-phase approach (**Figure 1**). In Phase 1, we focused on assessing how clinical trial sponsors defined and documented PDs prior to and during the COVID-19 pandemic. We collected sponsor representatives' perceptions of the impact of the pandemic on PDs, as well as information related to trial activations and closures, mitigation strategies, and rates of adverse events. The information derived from Phase 1 will inform the design of Phase 2, in which we will conduct a meta-analysis that explicitly examines the direct impacts of the mitigation strategies on PDs, other key metrics of data quality, and patient access to clinical trials. Phase 2 will also address other pertinent research questions raised in the Phase 1 evaluation. This discussion document presents the preliminary results from Phase 1 of the project and outlines our plans for Phase 2.

**Figure 1: Overall project approach.**



## Phase I: Define Parameters

### Phase I Aims

The aims of Phase I were to describe:

- Pre-COVID-19 pandemic PDs and the associated documentation requirements.
- Changes that occurred to PD descriptions, documentation requirements for PDs, and volume of PDs during the COVID-19 pandemic.
- Trial Sponsors' perception of the impact of shifting PD descriptions, documentation requirements, and volume of PDs on trial data integrity and missingness.
- Whether trial sponsors have retained or intend to retain any COVID-19 pandemic-era changes to their PD design or documentation processes moving forward.

### Phase I Approach

ASCO and *Friends* first surveyed, and then interviewed, both industry and NCI cooperative group sponsors of anti-cancer interventional trials to understand changes to their clinical trial protocols during the COVID-19 pandemic. (A full list of survey and interview questions can be found in Appendices A-C.) Participating sponsor organizations were identified based on previous interaction with ASCO and *Friends* research activities, but all industry and NCI cooperative group sponsors who oversaw anti-cancer treatment trials (Phase 1, 2, or 3) evaluating any modality that were open in the United States between January 2015 and May 2022 were eligible to participate. Participation in the project was voluntary and at the discretion of the sponsor.

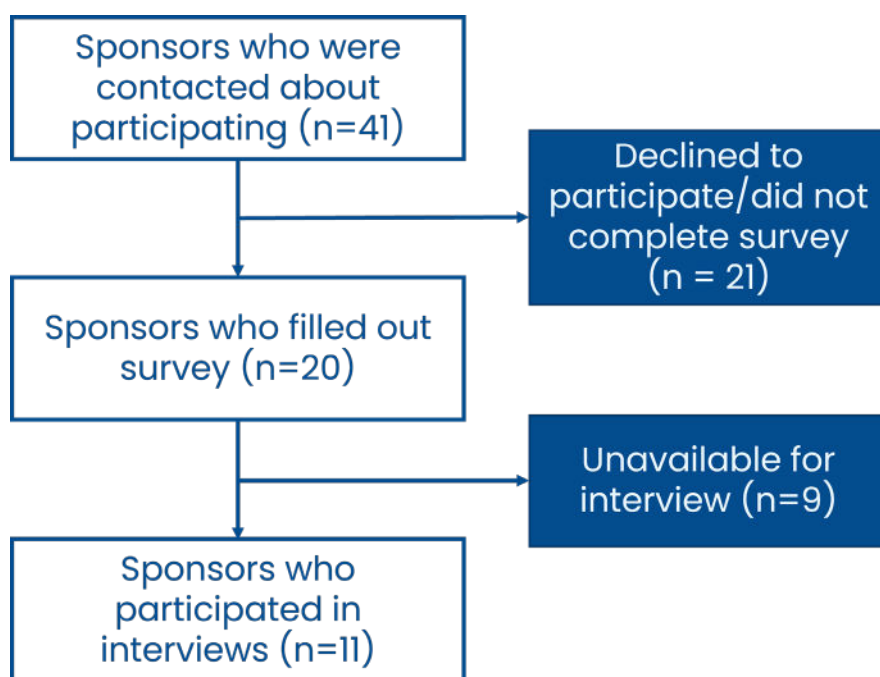
The study design was submitted for IRB review and was classified as exempt research. The survey and interview tools were created by ASCO and *Friends* staff and reviewed by the Task Force. After reviewing the study material, sponsor organizations (either industry or NCI cooperative groups) selected their own participants (henceforth, "Sponsors") to be surveyed and interviewed for the study.

The Task Force reviewed de-identified survey findings from each sponsor organization to identify areas for further exploration during semi-structured interviews. The interviews were conducted virtually over Zoom by an ASCO or *Friends* staff person with high-level oncology trial operations and data management personnel from a sample of the sponsor organizations. Sponsors received the discussion guide before the Zoom call and initial questions were the same for all participants; however, follow-up questions varied based on the discussion. During these interviews, Sponsors elaborated on their survey results and discussed their perceptions of the impact of PDs, other trial modifications, and mitigation strategies implemented during the COVID-19 pandemic.

Data collection was limited to May to July 2022 for surveys and July to October 2022 for interviews; thus, the participant sample does not include all sponsor organizations that met the eligibility criteria (**Figure 2**). Twenty sponsors (49% of those contacted) completed the survey for analysis and a subset of 11 sponsors (55% of those who completed surveys) were interviewed.

Interview findings suggested interpretation of study findings would benefit from speaking with leadership in the NCI's Cancer Therapy Evaluation Program (CTEP) about their processes for preparing and disseminating guidance during the pandemic. As such, representatives from NCI's CTEP were also interviewed using a modified version of the sponsor interview guide. Only aggregated, de-identified findings were shared with the Task Force.

**Figure 2: Consort diagram of the approach for including sponsors organizations who participated in the analysis.**



## Findings from Phase 1

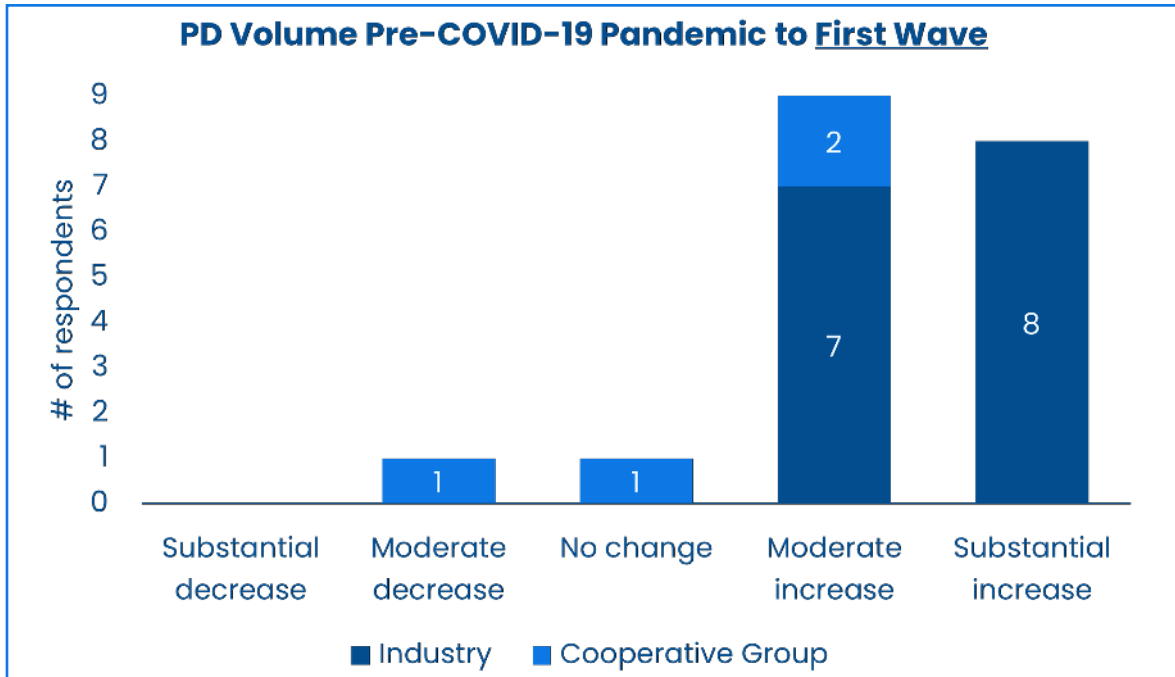
All findings reported below are based on information provided by Sponsors in surveys and interviews.

### Sponsors' Perceived Impacts of the COVID-19 Pandemic

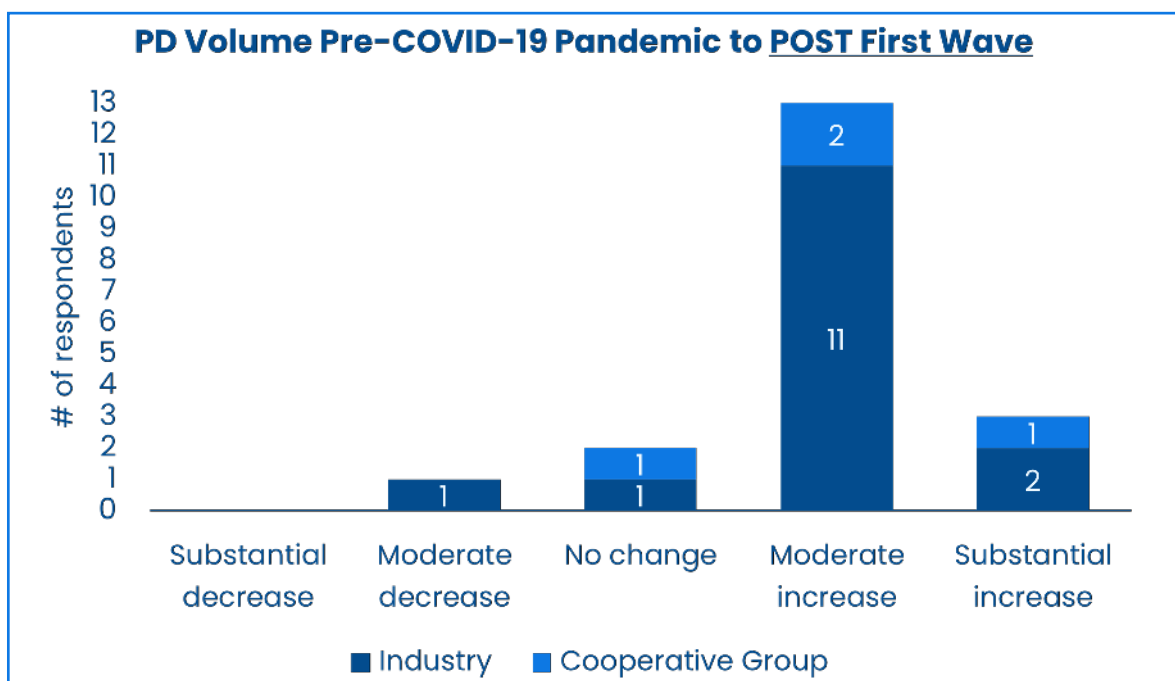
As has been previously reported, trials were most impacted early in the pandemic.<sup>3,4</sup> Sponsors reported an increase in PD volume in the first wave of the COVID-19 pandemic (March-April 2020) (**Figure 3**). After the initial wave (starting in May 2020), the increase in PD volume compared to the pre-pandemic period was slightly lower (**Figure 4**). In the survey, 85% (17/20) of Sponsors reported that there was no change in how many trials closed due to low accrual since the start of the COVID-19 pandemic. While some Sponsors closed trial sites early in the pandemic for any reason related to pandemic mitigation strategies, others reported when interviewed that their sites remained open. Some interview participants specified that, during the early phases of the pandemic, very sick patients (e.g., children or patients with late-stage disease) were mostly likely to continue attending in-person appointments.



**Figure 3: Change in PD volume pre-COVID-19 Pandemic to first wave.** Sponsors were asked about the change in PD volume before the COVID-19 Pandemic to the first wave of the COVID-19 Pandemic (March-April 2020). Results are reported by Industry vs. Cooperative Group Sponsors. (One sponsor did not respond.)

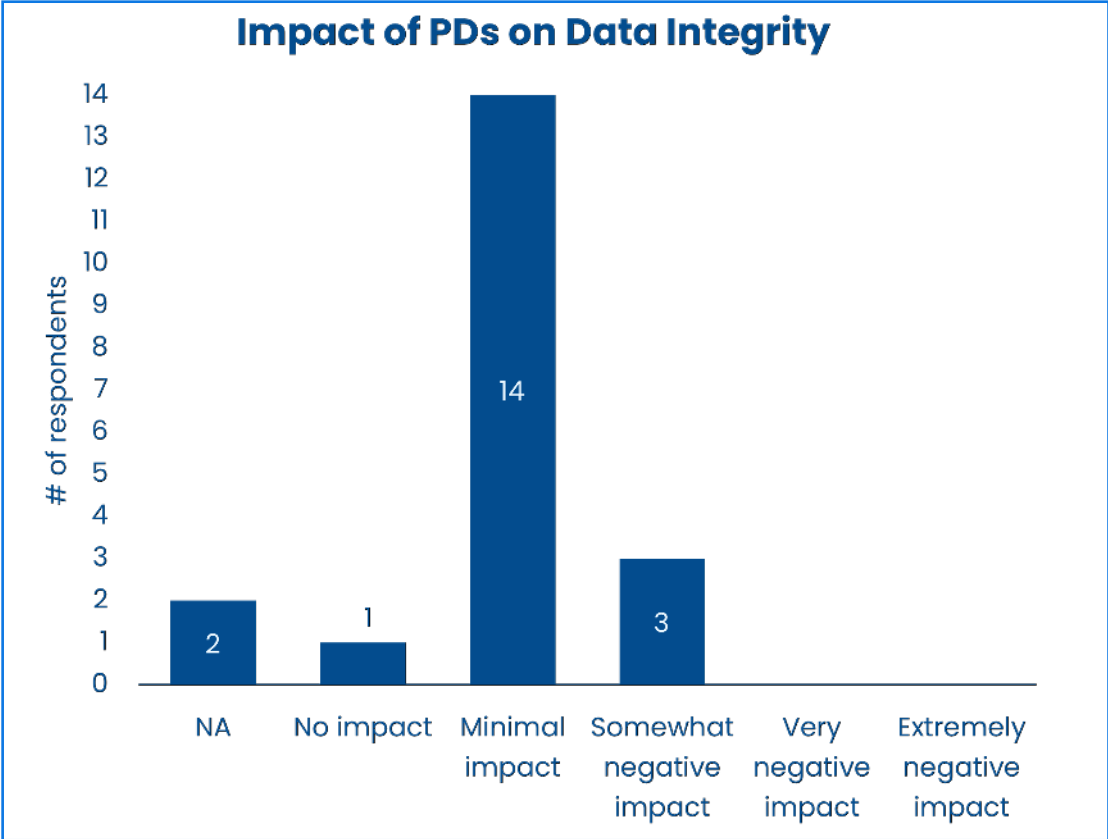


**Figure 4: Change in PD volume pre-COVID-19 Pandemic to post-first wave.** Sponsors were asked about the change in PD volume before the COVID-19 Pandemic to after the first wave of the COVID-19 Pandemic (May 2020 and beyond). Results are reported by Industry vs. Cooperative Group Sponsors. (One sponsor did not respond.)



In interviews, most Sponsors reported that the COVID-19 pandemic had only a minor impact on clinical trials after May 2020, which they attributed to U.S. sites pivoting quickly to allow most patients already enrolled on studies to continue with few disruptions due to flexibilities. Survey data showed that most Sponsors perceived a minimal impact of the PDs during the pandemic on data integrity (**Figure 5**). However, many Sponsors reported persistent lags in data entry related to staff shortages or turnover at trial sites. They reported that time delays were more common than data quality issues.

**Figure 5: PD impact on data integrity.** In the survey, sponsors were asked to rate the impact level to overall data integrity of PDs during the pandemic and provided with 5 responses ranging from “No Impact” to “Extremely Negative Impact.”



**PDs During the COVID-19 Pandemic**

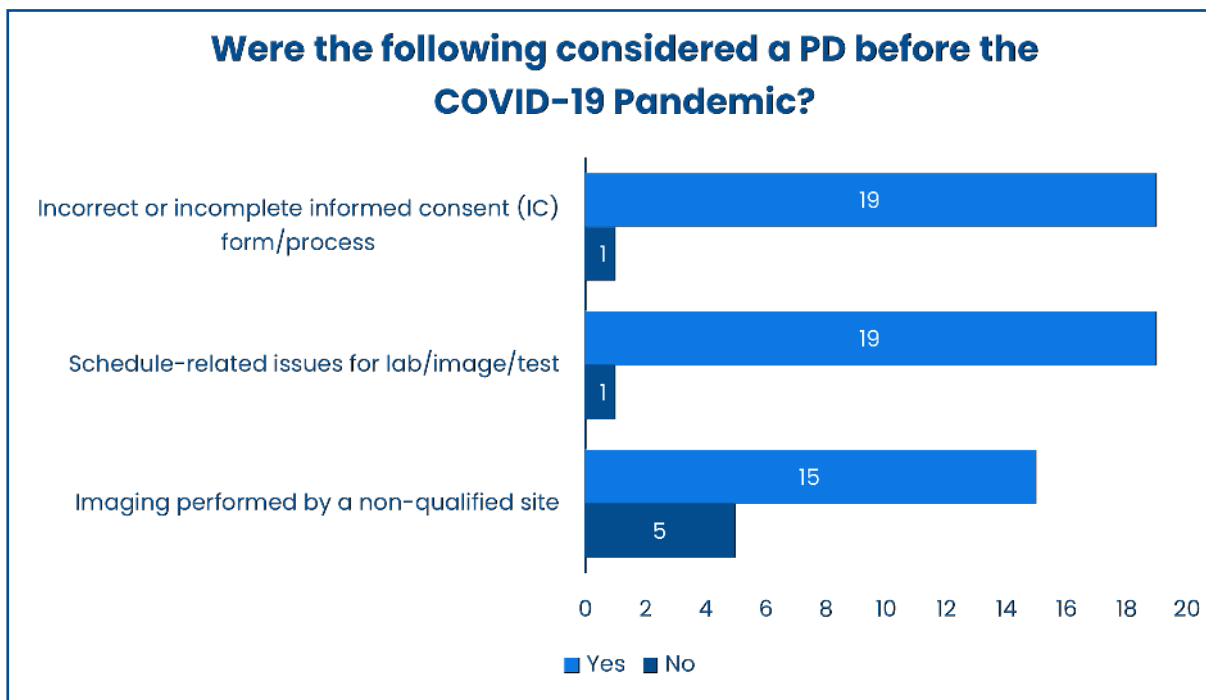
Nearly all sponsors (95%) flagged COVID-19 pandemic-specific PDs. However, this data is often only shared with regulators when requested (i.e., during a submission). For Sponsors who analyzed the types of PDs, they reported minimal differences in the types of PDs by different trial characteristics (e.g., disease type or patient population). Sponsors observed more PDs in later phase trials, which typically have more patients and longer follow-up periods. Missed or out-of-window visits and assessments were most common early in the pandemic when patients were not traveling either due to COVID-19 pandemic restrictions or concerns about becoming ill from COVID-19, but these are no longer a prevalent challenge.



### Remote Patient Monitoring

The COVID-19 pandemic accelerated the trend to make clinical trials more flexible for patients and providers through the incorporation of remote patient monitoring. Examples of frequently implemented remote patient monitoring include remote distribution of oral medication, imaging or blood draws at local facilities, remote informed consent discussion, and telemedicine visits. Many of these were classified as PDs before the pandemic (**Figure 6**). In interviews, it became apparent that part of the adaption to the COVID-19 pandemic was to incorporate remote patient monitoring activities into trial protocols, rather than to include them as PDs.

**Figure 6: Pre-COVID-19 Pandemic PD definitions.** In the survey, sponsors were asked to rate the impact level to overall data integrity of PDs during the pandemic and provided with 5 responses ranging from “No Impact” to “Extremely Negative Impact.”



Many Sponsors reported that they are considering opportunities to retain remote patient monitoring in trials moving forward, although some noted that not all flexibilities will continue. Those Sponsors who plan to retain remote patient monitoring indicated that, in the right context, it can ease patient burden while still collecting necessary data. Some Sponsors perceived that investigators may be resistant to continuing remote monitoring due to decreased oversight of their trial participants. Many highlighted that when they plan to include flexibilities for remote monitoring in their trial protocols, it would be considered optional rather than a required approach. Guidance from FDA and NCI informed modifications to trials early in the pandemic and may help shape Sponsor decisions about maintaining changes moving forward.



## **Guidance from Regulators and NCI**

In interviews, many Sponsors indicated that guidance provided by regulators and the NCI helped facilitate the ongoing conduct of cancer clinical trials during the pandemic. Cooperative group interviewees reported that they were well-positioned to adapt to the pandemic quickly alongside NCI due to pre-existing mechanisms of communication with CTEP leadership. Industry Sponsors indicated that guidance documents from FDA (and global regulatory bodies, as relevant) were their primary reference points for clinical trial conduct. According to Sponsors, the timeliness of guidance documents from FDA and NCI was essential to mitigating the pandemic's negative effects on trials and patients, particularly early in the pandemic. At that time, FDA was permitted to bypass the usual requirements for guidance oversight and issue guidance rapidly, and NCI produced guidance documents through internal coordination. Some industry Sponsors commented that ongoing challenges outside of the U.S. – whether pandemic-related or otherwise – continue to impact regulatory guidance for global studies, and by extension, trial design and operations.

## **Flexibilities in the Future**

Sponsors continue to evaluate which flexibilities they will retain in their interventional treatment trial protocols beyond the COVID-19 pandemic. Our findings from Phase 1 demonstrate variability among Sponsors in their approach to incorporating flexibilities; some readily adopted the strategies, while others – uncertain about whether the allowances will be permanent – have been more hesitant. Some Sponsors expressed concern about potential limitations on trial data quality with remote patient monitoring (e.g., local labs, remote auditing), while others found that these concerns diminished after flexibilities were introduced. Our hope is that findings to date and the analysis for Phase 2 will help sponsors make decisions about the appropriateness and value of bringing these flexibilities into the future.

## **Phase 2: Determine Impact**

The Phase 1 portion of the evaluation used semi-quantitative survey data and Sponsor interviews to provide initial insights into the impact of the COVID-19 pandemic on trial conduct, and to generate hypotheses for more detailed evaluation in Phase 2. Although the focus of Phase 1 was on PDs, other domains were also evaluated including the number of active trials, trial initiations, and trial closures over time; eligibility and consent related changes; assessment, lab, and imaging changes, mitigation strategies adopted; and patterns of adverse events. Moreover, the Sponsor interviews and discussions with NCI's CTEP indicated that a more extensive and inclusive evaluation framework would be informative, which includes a detailed understanding of trial access during the pandemic and whether the pandemic affected the enrollment of diverse populations to trials. Phase 2 may include different and/or additional Sponsors from Phase 1 if the eligibility requirements are met.

### **Phase 2 Aims**

The aim of Phase 2 is to test the hypotheses derived from Phase 1. Thus, for Phase 2, participating Sponsors will be asked to provide aggregate estimates of the key data domains highlighted by the Phase 1 evaluation as necessary to support a more determinative inference about the impact of the mitigation strategies used during the pandemic. Recognizing that participating Sponsors may have resource constraints, our aim is to request a limited, homogenous set of

data from all Sponsors to facilitate aggregate analyses and to limit the demands on Sponsor resources.

With these considerations in mind, the specific aims of Phase 2 are to characterize, over time in relation to the COVID-19 pandemic:

- The number of PDs (average per patient)
- The number of each type of PD (overall)
- Total enrollments per month to the sponsor portfolios of trials
- Grade 1 or 2 and grades 3 or 4 adverse events (average per trial)
- The number of dropouts (average per patient)
- Time delays

As suggested by the information obtained from Phase 1, an additional aim will be to examine the above outcomes from the perspective of diverse enrollment. Thus, for instance, one concern might be that the changes to trial conduct wrought by the pandemic might differentially impact sociodemographically underrepresented groups, who, for instance, might have experienced more PDs than their counterparts. Thus, for each outcome above, we will further request that Sponsors provide both overall estimates and estimates by categories of sex, age (<65 vs. 65 or older), race (Black vs. Asian vs. White vs. other) and ethnicity (Hispanic vs. not Hispanic).

Further, patterns of outcomes may differ by the nature of the trials, which could also influence the overall assessment of the impact of the pandemic on trial conduct. Thus, we will examine whether the outcomes noted above differ by study level variables (cancer type, study phase, and stage (advanced vs. adjuvant disease)).

We also plan to request the number, type, and date of implementation of mitigation strategies adopted by each sponsor during the initial pandemic wave, to determine whether the volume of strategies that were adopted is also correlated with outcomes.

Finally, as noted in Phase 1, we will represent the findings overall among all Sponsors, and also disaggregated according to sponsor type (industry vs. NCI sponsored cooperative groups). To evaluate these data, a meta-analytic approach will be used. This statistical approach requires the collection of only aggregate (deidentified) single measures for each measurement domain from each sponsor and will allow us to derive the overall average tendency (i.e., point estimates) across the trial system and to simultaneously understand accompanying variability across a diverse set of sponsors. Differences in patterns by demographic and study level variables will be examined using moderator analyses. This strategy has the distinct advantage of requiring the collection of only deidentified single measures for each measurement domain from each Sponsor but is limited by the lack of patient-level data to address within-patient patterns.

## Conclusions and Next Steps

The COVID-19 pandemic impacted the conduct of cancer clinical trials and has likely accelerated a trend towards greater flexibility in trial conduct that was already emerging. The strategies implemented during the COVID-19 pandemic to provide greater flexibility in the execution of trial regulatory procedures, patient evaluation and data ascertainment can minimize clinical trial complexity, leading to reduced burden on sites and patients and improved access. Sponsors continue to include flexibilities in new protocols as they deem appropriate and engage sites and investigators in the process, while following regulatory guidance.

To date, the primary aim of the Task Force has been to derive preliminary insights about the influence of the COVID-19 pandemic on trial conduct. In Phase 1 of this evaluation, sponsors reported that in their judgement, the mitigation strategies adopted in the face of the pandemic did not greatly impact data integrity. However, there is a recognition that a more detailed, quantitative, and statistical evaluation of clinical trial data integrity may provide greater and more determinative insight. We anticipate that the insights derived, and the hypotheses generated, from the Phase 1 portion of our evaluation will appropriately inform the conduct of our Phase 2 evaluation, in order to ultimately help guide the cancer clinical trial community about next steps in advancing the science of clinical trial conduct.

## References

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## Appendix A – Survey Instrument

### Definitions

- **Protocol Deviation (PD):** Any non-compliance with Institutional Review Board (IRB)-approved protocol, including prospectively approved deviations or waivers.
- **Significant or Serious Protocol Deviation:** A protocol deviation which increases potential risk to participants or affects the integrity of study data. An isolated deviation may not be significant by itself, but significance may increase with numerous deviations of the same nature.
- **Mitigation Strategy:** Depending on the severity or frequency of one or more protocol deviations, the site may be expected to define a mitigation strategy (sometimes referred to as a Corrective and Preventive Actions (CAPA)). This strategy is broken into two parts:
  - ◊ **Corrective Action (CA),** which is the action the site takes to address the deviation. Examples of corrective actions include (but are not limited to): notifying the affected participant(s) and protocol team; re-consenting the participant(s); completing missed procedures; repeating laboratory tests; completing additional participant monitoring or management procedures; and/or destroying specimens collected in error.
  - ◊ **Preventive Action (PA),** which is the action the site takes in attempt to prevent recurrence of the product or quality problem moving forward. Examples of preventive actions include (but are not limited to): discussion of the deviation with relevant study staff, refresher training of study staff; review and/or revision of documents outlining Standard Operating Procedures (SOPs) or other study implementation materials; development of new study implementation materials; implementation of additional communication, Quality Control (QC)/ Quality Assurance (QA), or oversight/supervisory procedures; changes in day-to-day workflow; and/or changes in general participant management or laboratory procedures.
- **Remote:** Geographically separated from the research site administering the clinical trial.

### Pandemic-Related Time Periods

- Pre-COVID: January 2015 through December 2019.
- Immediately Pre-COVID: January and February of 2020.
- First Wave: March and April of 2020.
- Post-First Wave: May 2020 to May 2022.

Note: All questions refer to interventional anti-cancer trials (phase 1, 2 or 3) involving any modality (e.g., systemic therapy [cytotoxic, immune, hormonal, targeted, etc.], surgery, radiation, etc.) sponsored by your organization that are/were open in the United States.

### Begin Survey:

#### Section 1 – Cancer Treatment Trial Portfolio

##### *Cancer trials underway immediately pre-COVID-19 pandemic (January and February 2020)*

1. How many interventional Phase 1 anti-cancer trials did your organization have ongoing in January 2020?
  - 0
  - 1-2
  - 3-5
  - 6-10
  - 11-20
  - 20-50
  - More than 50

2. How many interventional Phase 2 anti-cancer trials did your organization have ongoing in January 2020?
  - 0
  - 1-2
  - 3-5
  - 6-10
  - 11-20
  - 20-50
  - More than 50
  
3. How many interventional Phase 3 anti-cancer trials did your organization have ongoing in January 2020?
  - 0
  - 1-2
  - 3-5
  - 6-10
  - 11-20
  - 20-50
  - More than 50

***Cancer trials opened during the COVID-19 pandemic (March 2020 to May 2022)***

4. How many interventional Phase 1 anti-cancer trials has your organization opened since March 2020?
  - 0
  - 1-2
  - 3-5
  - 6-10
  - 11-20
  - 20-50
  - More than 50
  
5. How many interventional Phase 2 anti-cancer trials has your organization opened since March 2020?
  - 0
  - 1-2
  - 3-5
  - 6-10
  - 11-20
  - 20-50
  - More than 50
  
6. How many interventional Phase 3 anti-cancer trials has your organization opened since March 2020?
  - 0
  - 1-2
  - 3-5
  - 6-10
  - 11-20
  - 20-50
  - More than 50



***Cancer trials underway during the first wave of the COVID-19 pandemic (March and April of 2020)***

7. How would you characterize the impact of trial holds at sites during the first wave of the pandemic (March 2020–May 2020) on those trials?
  - None/few (0–25%) of our trials were delayed or otherwise impacted by holds
  - Some (26–50%) of our trials were delayed or otherwise impacted by holds
  - Most (51–75%) of our trials were delayed or otherwise impacted by holds
  - Nearly all/all (>76%) of our trials were delayed or otherwise impacted by holds
8. What was the approximate average hold time at sites during the March 2020–May 2020 period? \_\_\_ (weeks)
9. How would you characterize the impact of trial closures at sites during the first wave of the pandemic (March 2020–May 2020) on those trials?
  - None/few (0–25%) of our trials were negatively impacted by closures
  - Some (26–50%) of our trials were negatively impacted by closures
  - Most (51–75%) of our trials were negatively impacted by closures
  - Nearly all/all (>76%) of our trials were negatively impacted by closures
10. Do you have any additional comments regarding trial holds and closures during the first wave of the pandemic?

***Cancer trials underway post-first wave of the COVID-19 pandemic (May 2020 to May 2022)***

11. Compared to the March 2020–May 2020 period (your answer to question 7), how would you characterize the impact of trial holds at sites on your organization’s interventional anti-cancer trials after May 2020 and up to the current date?
  - The percentage of trials delayed or otherwise impacted by holds was much lower
  - The percentage of trials delayed or otherwise impacted by holds was somewhat lower
  - The percentage of trials delayed or otherwise impacted by holds was the same
  - The percentage of trials delayed or otherwise impacted by holds was somewhat higher
  - The percentage of trials delayed or otherwise impacted by holds was much higher
12. Compared to the March 2020–May 2020 period (your answer to question 9), how would you characterize the impact of trial closures at sites on your organization’s interventional anti-cancer trials after May 2020 and up to the current date?
  - The percentage of trials negatively impacted by closures was much lower
  - The percentage of trials negatively impacted by closures was somewhat lower
  - The percentage of trials negatively impacted by closures was the same
  - The percentage of trials negatively impacted by closures was somewhat higher
  - The percentage of trials negatively impacted by closures was much higher
13. Do you have any additional comments regarding trial holds and closures from May 2020 to May 2022?

**Section 2 – Organizational Definitions**

14. Please provide your organization’s definition of a “major PD” (sometimes called a “serious PD”): \_\_\_
15. What types of major, significant, or serious PDs have been the most common during the COVID-19 pandemic? \_\_\_

16. Please provide your organization's definition of a "minor PD": \_\_\_
17. What types of minor PDs have been most common during the COVID-19 pandemic? \_\_\_

### Section 3 – Pre-COVID-19 PDs

18. During the pre-COVID-19 period (January 2015 through December 2019), did your organization typically categorize eligibility and consent issues as PDs? E.g., participant did not meet eligibility criteria, incorrect or incomplete informed consent form/process, or re-consent not obtained as required.
- Yes
  - No
19. During the pre-COVID-19 period (January 2015–December 2019), which of the following eligibility or consent-related changes to a patient's protocol-specified treatment plan were typically defined as a PD? [select all that apply]
- Participant did not meet eligibility criteria
  - Incorrect or incomplete informed consent (IC) form/process, including:
    - ◊ Consent form document not signed/dated by study participant or parent/legally authorized representative (if applicable); signed incorrect IRB-approved version of IC form; IC form does not contain all required signatures; IC form signed after registration/enrollment; signed IC form version that was not protocol specific; patient/study participant signed IC form containing changes not approved by the CIRB/IRB; non-English speaker signed untranslated version of IC form; or did not document IC process
  - Re-consent not obtained as required
20. During the pre-COVID-19 period (January 2015–December 2019), which of the following treatment-related changes to a patient's protocol-specified treatment plan were typically defined as a PD? [select all that apply]
- Failure to follow trial randomization
  - Failure to discontinue treatment
  - Administration of non-protocol defined therapy to treat subject's disease or concomitant medication used was not permitted per protocol
  - SAE reported out of window
  - Dosing issues, including agent-related issues and:
    - ◊ Study agent administered to wrong patient/study participant; Study-supplied agent substituted with non-study-supplied agent, including commercial agent; Study agent stored incorrectly; Study agent prepared incorrectly; Study agent prescribed by unauthorized prescriber
  - Device-related issues, including:
    - ◊ Study device administered to incorrect subject; Study device malfunction; or Study device not returned
21. During the pre-COVID-19 period (January 2015–December 2019), which of the following assessment, lab, or imaging-related changes to a patient's protocol-specified treatment plan were typically defined as a PD? [select all that apply]
- Schedule-related issues, including:
    - ◊ Baseline assessments are out of window; Delayed image submission; Timing of Lab/Image/Test/Procedure not per protocol
  - Physical assessment deviation
  - Patient does not have a safety follow-up as required
  - Lab/Imaging/Test/Procedure after withdrawal of consent



- Lab, imaging, or other test/procedure not done
- Imaging performed by a non-qualified site
- Other imaging-related issues, including:
  - ◊ Incorrect imaging agent administered; incorrect imaging agent dose administered; Incorrect injection to scan time; Incorrect imaging modality; Incomplete anatomical coverage; Imaging parameters not per protocol; Images lost/unavailable/corrupt; Images not submitted; Equipment not credentialed prior to imaging

## Section 4 – Volume of PDs during COVID-19 Pandemic

22. How did the average volume of PDs collected during the first wave of the pandemic (March 2020 and April 2020) compare to the pre-pandemic (January 2015–December 2019) volume?
- Substantial increase after March 2020
  - Moderate increase after March 2020
  - No measurable change after March 2020
  - Moderate decrease after March 2020
  - Substantial decrease after March 2020
23. How did the average volume of PDs collected post-first wave (starting May 1, 2020) compare to the pre-pandemic (January 2015–December 2019) volume?
- Substantial increase post-first wave
  - Moderate increase post-first wave
  - No measurable change post-first wave
  - Moderate decrease post-first wave
  - Substantial decrease post-first wave
24. Compared to pre-pandemic (January 2015 through December 2019), in May 2022 how had the average number of significant/serious PDs changed relative to the average number of minor PDs?
- Increased
  - Remained stable
  - Decreased

## Section 5 – PD Mitigation Strategies

25. Which of the following mitigation strategies had NOT been employed pre-COVID-19 pandemic (January 2015 through December 2019) and were introduced immediately prior to or during the pandemic (January 2020 to May 2022), at least in part to decrease the number of PDs? [select all that apply]
- Remote pre-screening for eligibility
  - Remote recruitment/trial education and counseling
  - E-consenting/remote informed consent
  - Remote routine lab testing
  - Remote study-specific lab testing
  - Remote study-required biopsies
  - Remote symptom monitoring for adverse events
  - Remote distribution of oral anticancer therapy
  - IV administration of investigational treatment outside of investigational site
  - Remote collection of patient-reported outcomes
  - Remote imaging (study-required baseline or follow-up)
  - Remote monitoring of long-term outcomes
  - Other (please describe)
  - None of the above
  - Please describe other mitigation strategies that were introduced: \_\_\_



26. Which of the following Corrective and Preventative Actions (CAPA) had NOT been employed pre-COVID-19 pandemic (January 2015 through December 2019) and were introduced immediately prior to or during the pandemic (January 2020 to May 2022), at least in part to decrease the number of PDs? [select all that apply]
- Notifying the affected participant(s) and protocol team of the deviation
  - Re-consenting the participants
  - Completing missed procedures
  - Repeating laboratory tests
  - Completing additional participant monitoring or management procedures
  - Destroying specimens collected in error
  - Discussion of deviations with relevant staff
  - Refresher training of study staff
  - Review and/or revision of Standard Operating Procedures (SOPs) or other study implementation materials
  - Implementation of additional communication
  - Quality Control (QC)/Quality Assurance (QA) or oversight/supervisory procedures
  - Changes in day-to-day workflow
  - Changes in general participant management or laboratory procedures
  - None of the above
  - Unknown

## Section 6 – Impacts on Patients and Data Collection

27. Does your organization collect/flag PDs that are attributable specifically to the COVID-19 pandemic?
- Yes
  - No
28. Do you have data on PDs that were requested by sites but not approved (by the IRB, DSMB, your organization, or other) during the COVID-19 Pandemic?
- Yes
  - No
29. PDs can be attributable to the study staff (e.g., missing a lab to be ordered) or the participant (i.e., skipping a scheduled visit). Do you have data on the proportion of PDs that are attributable to staff versus participant decision-making?
- Yes
  - No
30. Approximately what percentage of PDs are attributable to study staff (as opposed to participant decision-making)? \_\_\_
31. Have your organization's cancer treatment trial drop-out rates changed since the start of the COVID-19 Pandemic (March 2020)?
- Yes, drop-out rates increased during the pandemic and have not returned to pre-pandemic levels.
  - Yes, drop-out rates increased during the pandemic but have returned to pre-pandemic levels (or decreased further).
  - Yes, drop-out rates decreased during the pandemic and have not returned to pre-pandemic levels.
  - Yes, drop-out rates decreased during the pandemic but have returned to pre-pandemic levels (or increased further).
  - No change in drop-out rates was observed during the pandemic.



32. Has there been a change in how many of your organization's cancer treatment trials closed due to low accrual since the start of the COVID-19 Pandemic (March 2020)?
- Yes, there was an increase in how many trials closed due to low accrual during the pandemic and these closures have not returned to pre-pandemic levels.
  - Yes, there was an increase in how many trials closed due to low accrual during the pandemic but these closures have returned to pre-pandemic levels (or decreased further).
  - Yes, there was a decrease in how many trials closed due to low accrual during the pandemic and these closures have not returned to pre-pandemic levels.
  - Yes, there was a decrease in how many trials closed due to low accrual during the pandemic but these closures have returned to pre-pandemic levels (or increased further).
  - No change was observed during the pandemic.
33. Did rates of reported grade 1-2 adverse events (AEs) change during the pandemic?
- Yes, rates of reported grade 1-2 AEs increased during the pandemic and have not returned to pre-pandemic levels.
  - Yes, rates of reported grade 1-2 AEs increased during the pandemic but have returned to pre-pandemic levels (or decreased further).
  - Yes, rates of reported grade 1-2 AEs decreased during the pandemic and have not returned to pre-pandemic levels.
  - Yes, rates of reported grade 1-2 AEs decreased during the pandemic but have returned to pre-pandemic levels (or increased further).
  - No change in rates of reported grade 1-2 AEs was observed during the pandemic.
34. Did rates of reported grade 3-4 AEs change during the pandemic?
- Yes, rates of reported grade 3-4 AEs increased during the pandemic and have not returned to pre-pandemic levels.
  - Yes, rates of reported grade 3-4 AEs increased during the pandemic but have returned to pre-pandemic levels (or decreased further).
  - Yes, rates of reported grade 3-4 AEs decreased during the pandemic and have not returned to pre-pandemic levels.
  - Yes, rates of reported grade 3-4 AEs decreased during the pandemic but have returned to pre-pandemic levels (or increased further).
  - No change in rates of reported grade 3-4 AEs was observed during the pandemic.
35. How would you rate the impact level to overall data integrity of PDs during the pandemic?
- Extremely negative impact
  - Very negative impact
  - Somewhat negative impact
  - Minimal impact
  - No impact

## Appendix B – Interview Guide for Sponsors

### Introduction

Following recommendations made by the American Society of Clinical Oncology (ASCO) in its 2020 Road to Recovery report, ASCO and Friends of Cancer Research (*Friends*) seek to identify opportunities for cancer clinical trial sponsors to simplify the conduct of clinical trials. Many stakeholders in the cancer research community recognize the opportunity to improve patient access and clinical trial operations by maintaining some of the flexibilities that were introduced during the COVID-19 pandemic. To better understand the impact of the changes wrought by the pandemic on the execution of trials, ASCO and *Friends* aim to characterize the extent to which protocol deviations (PDs) were experienced before and during the pandemic. In so doing, it may be possible to simplify, streamline, and standardize PD descriptions and data collection. , ASCO and *Friends* are conducting semi-structured interviews with sponsors about the impact of the COVID-19 pandemic on PDs in their anti-cancer treatment trials. De-identified findings from these interviews will be published in a peer-reviewed journal and will inform development of a quantitative analysis plan for the second phase of the study.

### Objectives

1. Describe pre-COVID-19 pandemic PDs and the associated documentation requirements.
2. Describe changes that occurred to PD descriptions, documentation requirements for PDs, and volume of PDs during the COVID-19 pandemic.
3. Describe the perceived impact of shifting PD descriptions, documentation requirements, and volume of PDs on trial data integrity and missingness.
4. Describe whether trial sponsors have retained or intend to retain any COVID-19-era changes to their PD design or documentation processes.

### Definitions

- **Protocol deviation (PD):** Any non-compliance with Institutional Review Board (IRB)-approved protocol, including prospectively approved deviations or waivers.
- **Pre-COVID timeframe:** January 2015–December 2019.
- **Immediately Pre-COVID:** January and February 2020
- **First wave of COVID pandemic:** March and April 2020.
- **Post-First Wave:** May 2020–May 2022.

### Scope

- Interventional anti-cancer interventional trials (phases 1, 2 or 3) involving any modality (e.g., systemic therapy [cytotoxic, immune, hormonal, targeted, etc.], surgery, radiation, etc.) open between January 2015 and the current date are included.
- Study design: A qualitative descriptive study using semi-structured interviews with trial sponsors.
- We will conduct interviews with high-level oncology trial operations representatives from pharmaceutical companies, the NCI cooperative groups, and CROs that had phase I-III interventional trials open prior to and during the COVID-19 pandemic.
- Themes and definitions identified during these interviews will inform a data analysis plan for future review of sponsor trial data.



Objective	Domain	Questions
1/2	PD descriptions and development	<ul style="list-style-type: none"> <li>What amendments has your organization made to trial protocols that were approved prior to the start of the COVID-19 pandemic to mitigate the number and/or types of PDs?               <ol style="list-style-type: none"> <li>What amendments were made to mitigate which type(s) of PDs?</li> </ol> </li> <li>Have new protocols written since the start of the COVID-19 pandemic (compared to pre-COVID-19 protocols) included changes to mitigate the number and/or types of PDs?</li> <li>Has your organization changed its protocol development process as a result of operational challenges and PDs during the pandemic? If yes, please describe? If no, why not?</li> </ul>
2	PD documentation	<ul style="list-style-type: none"> <li><i>[If the sponsor answered 'yes' to #27: "Has your organization been collecting/flagging COVID-specific PDs?"]</i> <ol style="list-style-type: none"> <li>If yes: Has this data been shared with FDA? How else has this data been used?</li> <li>If no: Why not?</li> </ol> </li> </ul>
1/2	Volume of PDs	<ul style="list-style-type: none"> <li><i>[If the sponsor runs Phase 1 and Phase 2/Phase 3 trials]</i> Has there been a difference in the volume of PDs in early phase trials versus later phase trials?</li> </ul>
1/2	Types of PDs	<ul style="list-style-type: none"> <li>How do the types of PDs now compare to the types seen pre-pandemic? E.g., are certain types of PDs more common now than pre-pandemic? Are PDs more common in certain trial types?</li> <li>How has the change in types of PDs impacted your clinical trial design?</li> <li><i>[If the sponsor has data on PDs that were requested but not approved]</i> What types of PDs were requested but not approved (by the IRB, sponsor, etc.), if any? What were the reasons for not approving, if provided?</li> <li>Have significant/serious or minor PDs increased more, relative to the other?</li> <li>PDs can be attributable to the study staff (e.g., missing a lab to be ordered) or the participant (i.e., skipping a scheduled visit). Do you have data on the proportion of PDs that are attributable to staff versus participant decision-making?</li> <li>Are you aware of whether staffing issues (e.g., shortages) have led to an increase in PDs?</li> </ul>
2/3	Impact on patients	<ul style="list-style-type: none"> <li>Did your organization change its cancer treatment trial eligibility criteria as a result of the COVID-19 pandemic?</li> <li>How have your trial accrual rates changed since the start of the pandemic (March 2020)? Since the end of the first wave (May 2020)?</li> </ul>
3	Impact on trial data	<ul style="list-style-type: none"> <li>Please elaborate on your response to survey question #35: "How would you rate the impact level to overall data integrity of PDs during the pandemic?" (1: Extremely negative impact to 5: No impact)</li> </ul>

Objective	Domain	Questions
2/3	Consultation with external stakeholders	<ul style="list-style-type: none"> <li>• Did your organization consult other stakeholders or guidance documents (e.g., regulators, public health agencies, trial sites, CROs, IRBs, patient groups, etc.) when making changes to <b>protocol development or amendment processes</b>?               <ul style="list-style-type: none"> <li>a) If so, who did you contact? Was this process for consulting the other stakeholders similar to what you had done before the pandemic?</li> </ul> </li> <li>• Did your organization consult other stakeholders or guidance documents (e.g., regulators, public health agencies, trial sites, CROs, IRBs, patient groups, etc.) when making changes to <b>PD documentation processes</b>?               <ul style="list-style-type: none"> <li>a) If so, who did you contact?</li> </ul> </li> <li>• Has your organization consulted with FDA or other regulatory agencies about the impact of PDs on <b>data integrity and missingness</b> during the pandemic?               <ul style="list-style-type: none"> <li>a) If so, what topics/strategies were discussed?</li> <li>b) If so, what changes did your organization make based on this consultation?</li> </ul> </li> </ul>
2/3/4	Future directions	<ul style="list-style-type: none"> <li>• Are changes to PD definition, development, or documentation processes made at the outset of the pandemic still in place?</li> <li>• Some changes that increased flexibility/reducing administrative burden may have the potential to impact data quality. Are there changes that were made that you think had essentially no impact on data quality and/or trial integrity? Were there changes that did have an impact?</li> <li>• Has your organization defined how it will retain changes to PD descriptions, development, or documentation processes?</li> <li>• How long do you anticipate keeping changes to your organization's PD documentation changes?</li> <li>• Is there anything else related to your organization's cancer treatment trial PD processes/strategies that you want to share?</li> </ul>

## Appendix C – Interview Guide for NCI

### Introduction

Following recommendations made by the American Society of Clinical Oncology (ASCO) in its 2020 Road to Recovery report, ASCO and Friends of Cancer Research (*Friends*) seek to identify opportunities for cancer clinical trial sponsors to simplify the conduct of clinical trials. Many stakeholders in the cancer research community recognize the opportunity to improve patient access and clinical trial operations by maintaining some of the flexibilities that were introduced during the COVID-19 pandemic. To better understand the impact of the changes wrought by the pandemic on the execution of trials, ASCO and *Friends* aim to characterize the extent to which protocol deviations (PDs) were experienced before and during the pandemic. In so doing, it may be possible to simplify, streamline, and standardize PD descriptions and data collection. ASCO and *Friends* are conducting semi-structured interviews with sponsors about the impact of the COVID-19 pandemic on PDs in their anti-cancer treatment trials. De-identified findings from these interviews will be published in a peer-reviewed journal and will inform development of a quantitative analysis plan for the second phase of the study.

### Objectives

1. Describe pre-COVID-19 pandemic PDs and the associated documentation requirements.
2. Describe changes that occurred to PD descriptions, documentation requirements for PDs, and volume of PDs during the COVID-19 pandemic.
3. Describe the perceived impact of shifting PD descriptions, documentation requirements, and volume of PDs on trial data integrity and missingness.
4. Describe whether trial sponsors have retained or intend to retain any COVID-19-era changes to their PD design or documentation processes.

### Scope

- Interventional anti-cancer interventional trials (phases 1, 2 or 3) involving any modality (e.g., systemic therapy [cytotoxic, immune, hormonal, targeted, etc.], surgery, radiation, etc.) open between January 2015 and the current date are included.

### Definitions

- *Protocol deviation (PD)*: Any non-compliance with Institutional Review Board (IRB)-approved protocol, including prospectively approved deviations or waivers.
- *Pre-COVID timeframe*: January 2015–December 2019.
- *Immediately Pre-COVID*: January and February 2020
- *First wave of COVID pandemic*: March and April 2020.
- *Post-First Wave*: May 2020–May 2022

### Study design

A qualitative descriptive study using semi-structured interviews with trial sponsors.

- We will conduct interviews with high-level oncology trial operations representatives from pharmaceutical companies and NCI cooperative groups that had phase I-III interventional trials open prior to and during the COVID-19 pandemic. Additionally, we will interview members of the NCI's CTEP.
- Themes and definitions identified during these interviews will inform a data analysis plan for future review of sponsor trial data.

NCI guidance documents: [Interim Guidance](#) (3/13/2020); [Updated Interim Guidance](#) (3/23/2020)

Objective	Questions
1/2	<ul style="list-style-type: none"> <li>• Pre-pandemic, how were PD documentation requirements determined? <ul style="list-style-type: none"> <li>◊ Oversight group? Process?</li> </ul> </li> <li>• How frequently were PD documentation requirements reviewed/updated?</li> <li>• Was this process updated during the pandemic? If so, how?</li> </ul>
2	<ul style="list-style-type: none"> <li>• Please describe the process for developing the interim guidance documents that were published in mid and late March 2020. I.e., <ul style="list-style-type: none"> <li>◊ How were the cooperative groups involved in drafting, if at all?</li> <li>◊ Which other stakeholders were involved in drafting, if any?</li> </ul> </li> </ul>
3	<ul style="list-style-type: none"> <li>• How would you characterize the impact of the pandemic on trial holds? <ul style="list-style-type: none"> <li>◊ During first wave (March and April 2020)? After?</li> </ul> </li> <li>• How would you characterize the impact of the pandemic on trial closures? <ul style="list-style-type: none"> <li>◊ During first wave (March and April 2020)? After?</li> </ul> </li> <li>• What impact did the pandemic have on accrual rates? <ul style="list-style-type: none"> <li>◊ During first wave (March and April 2020)? After?</li> <li>◊ To what extent do you attribute accrual rebounds (if seen) to the operational flexibilities that were introduced?</li> </ul> </li> <li>• How do the types of PDs now compare to the types seen pre-pandemic? <ul style="list-style-type: none"> <li>◊ Are certain types of PDs more common now than pre-pandemic?</li> <li>◊ Are PDs more common in certain trial types?</li> </ul> </li> </ul>
1/3	<ul style="list-style-type: none"> <li>• How does the volume of PDs now compare to the volume seen pre-pandemic? <ul style="list-style-type: none"> <li>◊ Are certain types of PDs more common now than pre-pandemic?</li> <li>◊ Are PDs more common in certain trial types?</li> </ul> </li> </ul>
3	<ul style="list-style-type: none"> <li>• How would you rate the impact level to overall data integrity of PDs during the pandemic? Did this differ by treatment type? Cancer type? Trial phase?</li> <li>• NCI asked the cooperative groups to flag COVID-related PDs (both major and minor). How have/will you use that data?</li> </ul>
4	<ul style="list-style-type: none"> <li>• Which operational changes introduced during the pandemic has the NCI chosen to retain moving forward? I.e., already incorporated into SOPs and to remain for the foreseeable future.</li> <li>• Which operational changes has the NCI chosen NOT to retain, and why?</li> <li>• What factors determine what is retained? Who is involved in decision-making?</li> </ul>
4	<ul style="list-style-type: none"> <li>• Which operational changes introduced during the pandemic is the NCI considering for retention moving forward? I.e., not yet incorporated into long-term SOPs, but may be.</li> <li>• What factors will determine what is retained? Who is involved in decision-making?</li> </ul>
	<ul style="list-style-type: none"> <li>• Is there anything else related to protocol deviations or protocol development that you think is relevant to share?</li> </ul>

