Clinical Trial Disruptions Due to COVID-19

An NCI perspective

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NISS Forum

July 21, 2020

DISCLAIMER

Adjustments to clinical trials processes were made expeditiously and in consultation with institutional leadership, IRBs, FDA, and study sponsors in order to **protect safety of patients, their families, and study personnel** amid the rapid emergence of COVID-19. Whether any of these changes or flexibilities could be adopted on a permanent basis has not been decided.

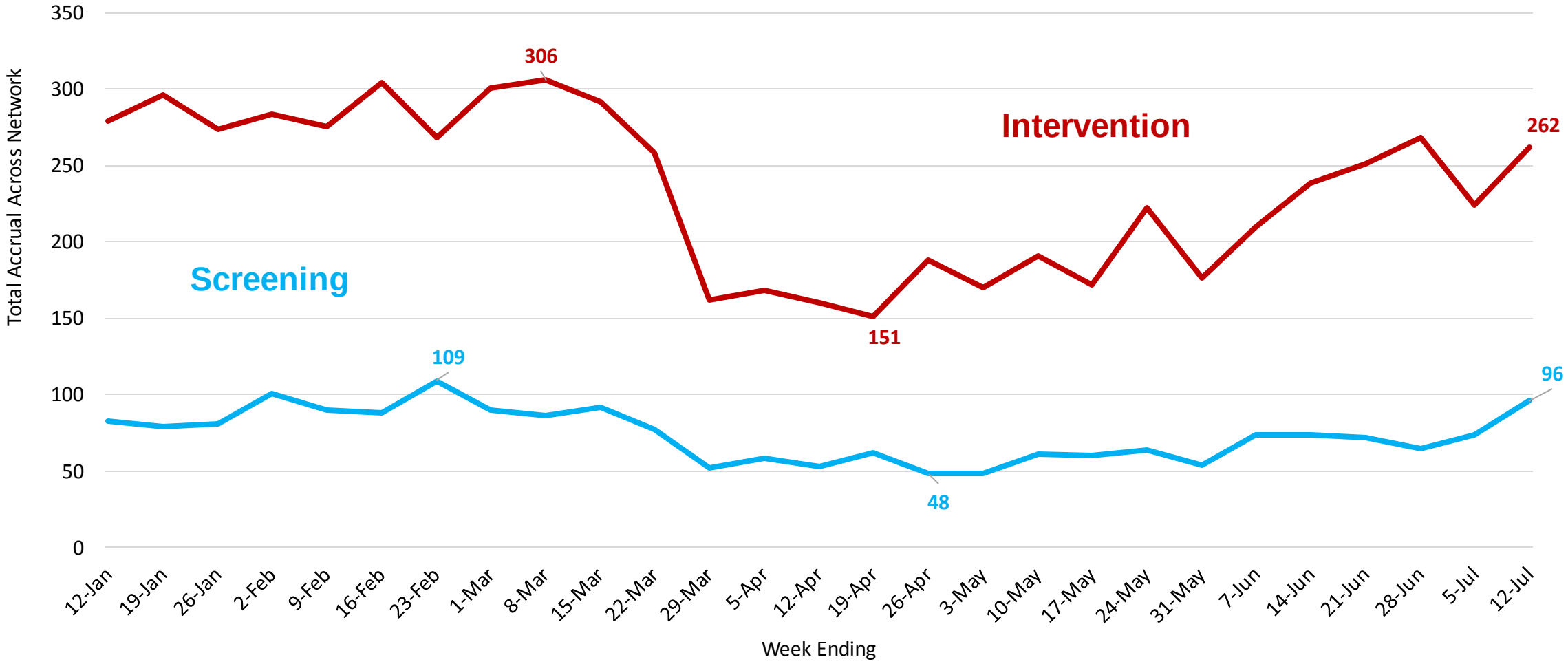
Outline

- Immediate consequences of pandemic surge and shutdowns
- Modifications to trial procedures
- Impact on study design and feasibility
- Leveraging expertise, trial resources and infrastructure, to learn about COVID-19 biology and its clinical impact, particularly on patients with cancer

Immediate consequences

- Substantial reduction in trial accrual for screening (e.g., genomic testing to determine eligibility) and intervention steps
- Clinics closed or reduced hours and staffing for “in-person” patient visits
- Patients unable or unwilling to come to the clinical trial site for clinical evaluations, treatment delivery (e.g., IV infusions, radiotherapy), specimen collections, etc.
- Many sites paused opening of new studies
  - Impact on patients with advanced cancer who may have exhausted therapy options outside of clinical trials

NCI National Clinical Trials Network (NCTN) Accrual for "Screening" and "Intervention" Steps by Week, January 6, 2020 to July 12, 2020



Provided courtesy of Dr. Meg Mooney, NCI, CTEP

Modified procedures

https://ctep.cancer.gov/investigatorResources/corona_virus_guidance.htm

- **Initial Interim Guidance on 3/13/2020**
  - Transfer of Patient's Care to a Different Participating Study Site
  - Continuity of Care Provided by Non-Research Staff (SOC therapy, labs, imaging, physical exams, vitals, performance status, standard assessments, blood collections)
  - Mailing of CTEP IND Oral Agents from Site Dispensing Pharmacy Directly to Patients
- **Additional Guidance on 3/23/2020**
  - Alternative Procedures for Ongoing Trials - Minor Protocol Deviations ("Virtual" study visits, reasonable delays in treatments, imaging, & lab tests, blood collections stored locally)
  - Alternative Procedures for Ongoing Trials – Major Protocol Deviations
  - Alternative Procedures for Auditing/Monitoring of Trials (modest audit delays; remote)
  - Alternative Procedures for Informed Consent for Trials (telephone remote IC)
  - Increased flexibility in mailing CTEP IND Oral Agents (risk/benefit for shipping)

Impact on study design, analysis, and feasibility

- Drops in accrual, if sustained, may adversely affect the feasibility of meeting target sample size in reasonable time period
- Timing and reliability of disease status and adverse event assessments may be affected if not performed per protocol at trial clinical sites by specially trained, experienced study investigators, using same imaging or specimen acquisition & processing procedures, etc.
- Risk:benefit balance related to trial participation might change

Impact on study design, analysis, and feasibility

- Accrual target with existing clinical sites no longer seen as feasible in reasonable time period (even after additional flexibilities implemented)
  - Open new clinical sites or try to boost accrual at sites less impacted by pandemic
  - Consider change in primary endpoint
  - Consider whether reduction in statistical power or precision might still yield meaningful results

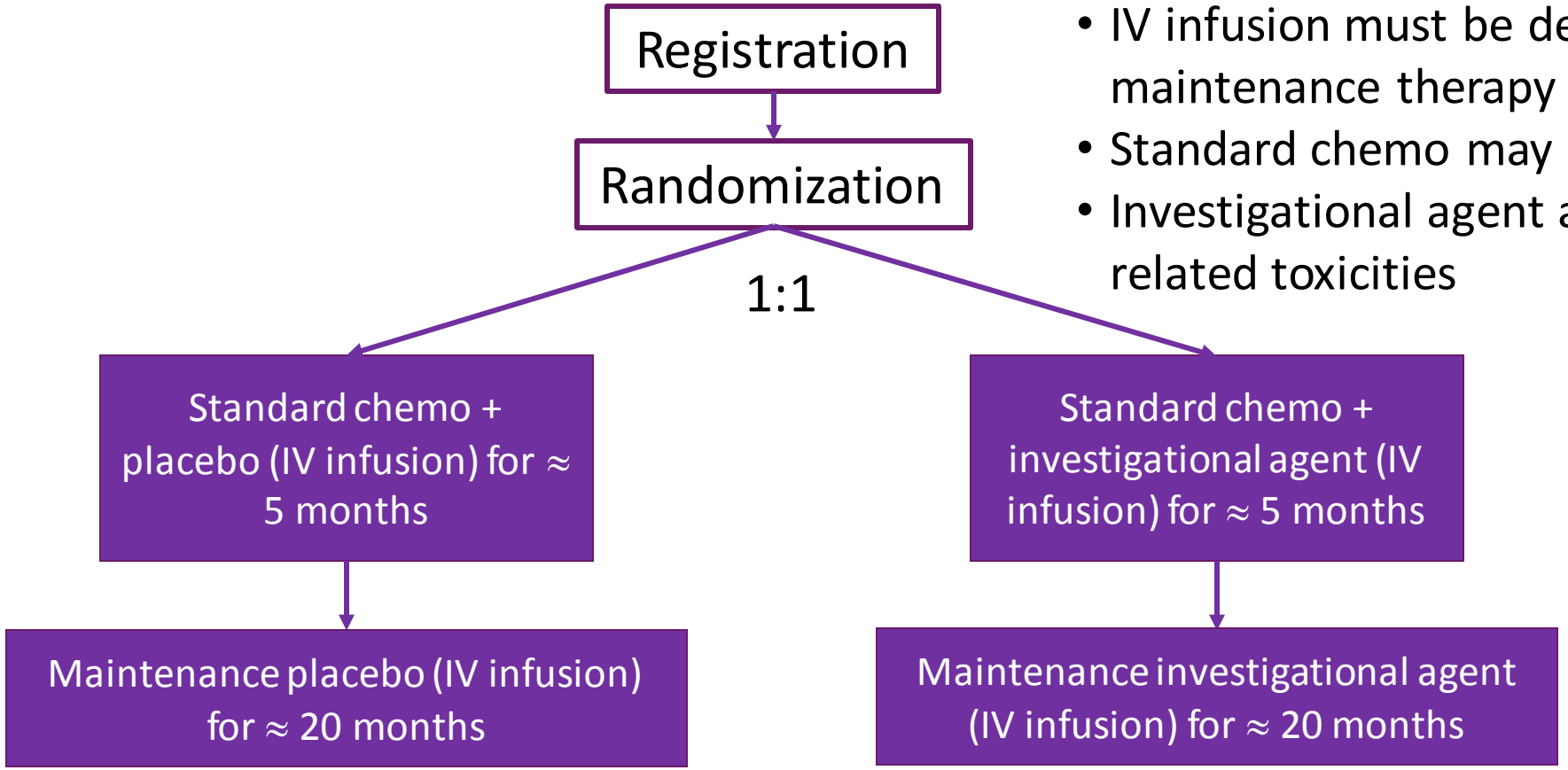
Impact on study design, analysis, and feasibility

- Timing and reliability of disease status, adverse event, and laboratory assessments may be affected if not performed per protocol at trial clinical sites by specially trained, experienced study investigators, using same specimen or imaging acquisition procedures, etc.
  - Maintain oversight by responsible study investigators through communication with local care providers
  - Provide training & instructions, specimens collection kits, etc. where feasible
  - Consider which laboratory assessments are robust, well standardized, and consistent across institutions or laboratories
  - Consider retrospective quality & reproducibility evaluations
  - Prepare to assess impact of added variability in study analyses

Impact on study design, analysis, and feasibility

- Reassessment of risk:benefit balance related to trial participation

  Example: Stratified randomized blinded placebo-controlled trial for patients with an advanced cancer



- Primary endpoint is progression-free survival (PFS)
- IV infusion must be delivered in clinic; maintenance therapy not standard of care
- Standard chemo may suppress immune system
- Investigational agent associated with immune-related toxicities

Impact on study design, analysis, and feasibility

- Reassessment of risk:benefit balance related to trial participation

  Example (cont.): Stratified randomized blinded placebo-controlled trial for patients with an advanced cancer

  CONCERN

  Due to current lack of reliable knowledge of risk for patients with cancer being infected and/or experiencing serious complications or death from COVID-19 (and ongoing uncertainty in the epidemic course), it was felt (at least by some) that adequate informed consent was not possible given the nontrivial unnecessary exposure for patients randomized to the placebo arm of this trial.

  STATUS

  Accrual has been suspended pending further discussion. Patients currently enrolled may opt to continue with blinded assigned treatment, or be unblinded and drop out.

Impact on study design, analysis, and feasibility

- Reassessment of risk:benefit balance related to trial participation

  Example (cont.): Stratified randomized blinded placebo-controlled trial for patients with an advanced cancer

Options under discussion (NCI, trial investigators, IRB, pharma partners)

- Make no changes and allow each patient to decide based on personal risk tolerance
  - Might be seen as potentially coercive
- Completely unblind the trial and remove maintenance placebo to lower risk of COVID-19 exposure for patients randomized to that arm
  - May require change of primary endpoint from PFS (susceptible to bias in unblinded study) to overall survival (OS)
  - Fewer OS event may lead to underpowered or infeasible study
- Allow choice of unblinding by clinical site
  - COVID-19 risks vary by region, but situation remains fluid
  - Complicates study analysis and interpretation

Leveraging expertise, trial resources and infrastructure

- Funding opportunities for cancer researchers to contribute to COVID-19 research (https://www.cancer.gov/research/key-initiatives/covid-19)
  - Much relevant expertise in biology and prevention of virus-associated cancers, and management of severe immune adverse effects of immunotherapies
- Leverage NCI clinical trials infrastructure (NCTN, ETCTN, NCORP) to rapidly accrue patients and collect longitudinal specimens for COVID-19 research
  - NCCAPS (NCT04387656) – Longitudinal study collecting blood samples, medical information, and medical images from patients being treated for cancer who test positive for SARS CoV-2 to characterize COVID-19 outcome in these patients, as well as COVID-19 effects on cancer treatment and outcomes
- Repurpose drugs to combat COVID-19 serious symptoms
  - TRC-10446 (NCT04370834) – Expanded access trial of tocilizumab (anti-IL-6 therapy) which is used in treating "cytokine storm" seen with some cancer immunotherapies

Summary remarks

- Lessons to be learned about necessity of some “standard approaches” in clinical trial conduct and monitoring vs. flexibility
  - May extend to routine clinical care (e.g., use of telehealth)
- Novel aspects to consider in benefit:risk assessment for clinical research
- Need to be attentive and nimble to adapt to continuously evolving landscape
- Demonstration of ability to rapidly develop and launch clinical studies
  - Value of standing clinical trials infrastructure, including biorepositories and laboratory networks
- Anticipate challenges in analysis and interpretation of some clinical trials affected by the COVID-19 pandemic

Acknowledgments

For providing background information and helpful suggestions in preparing this presentation

- Dr. Meg Mooney, Cancer Therapy Evaluation Program, DCTD, NCI
- Dr. Larry Rubinstein, Biometric Research Program, DCTD, NCI
- Dr. Boris Freidlin, Biometric Research Program, DCTD, NCI