Ingram Olkin Forum: Unplanned Clinical Trial Disruptions due to COVID-19 Examples from NHLBI-sponsored trials

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Examples from NHLBI-sponsored trials

The views expressed here are personal and may not reflect the views of NHLBI

A word about Ingram Olkin

- Professor of statistics at Stanford
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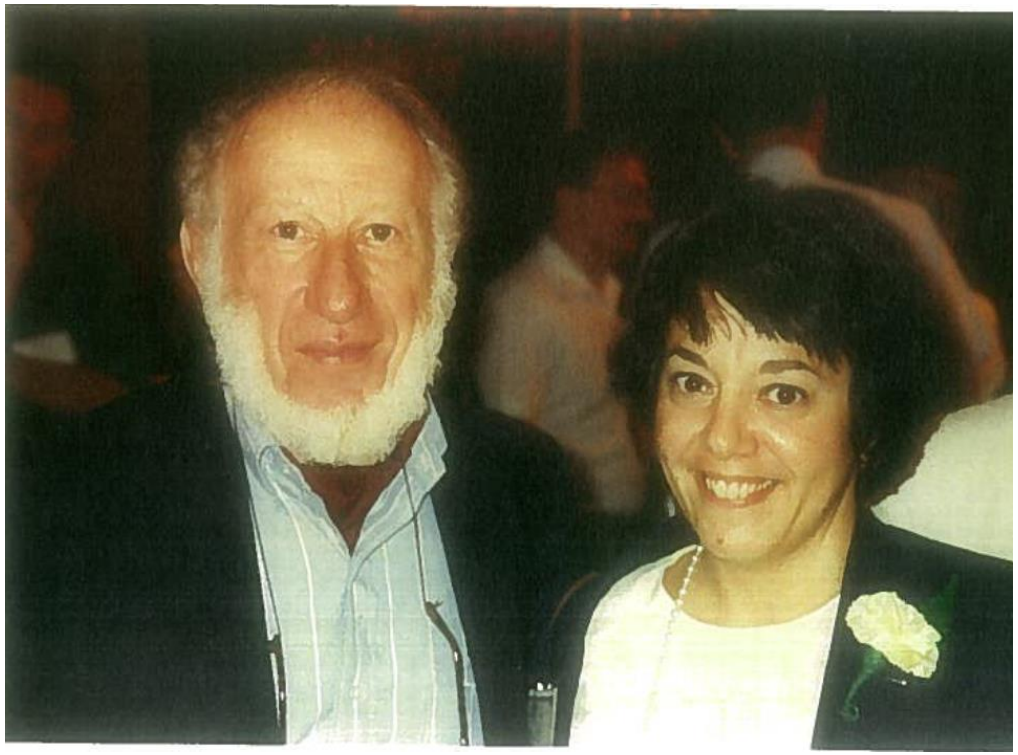

NISS Reception, JSM 2012

To the topic: Outline

- Factors affecting trial disruption due to a pandemic
  - When did disruption occur?
  - How far along was accrual at that time?
  - Nature of the intervention?
  - How will we modify the data collection and analysis?
- Example of a behavioral trial (accrual completed, intervention continuing)
- Example of treatment trials with long follow up: Bone Marrow Transplant Clinical Trials Network (BMT CTN) trials

Factors affecting trial disruption
(1) When did the disruption occur?

- It makes sense to establish a fixed date that the disruption began. This will make the data analysis easier.
- We use March 10, 2020. This is when accrual in most of our trials was halted.
- Some trials have reinstituted accrual and visits by now, but whether or not these are happening is center dependent.

Factors affecting trial disruption
(2) How far along was accrual?

- Easiest: accrual complete; only follow up is needed.
- Harder and harder as more accrual is needed.
- Difficult to restart accrual after a trial has been interrupted
    - If accrual is (say) 80% complete maybe that will suffice. (Reassess power and increased difference to be detected and agree that that is sufficient). This will require a protocol amendment (less hassle than restarting accrual).
    - If accrual has lagged all along, tolerance is probably not the best strategy for the funding agency.

Factors affecting trial disruption
(2) How far along was accrual (continued)?

- For those trials which are midway in accrual, accrual will be restarted, but may be slow or unsuccessful altogether.
- For funded trials in the planning stage on March 10, these will start, but problems with accrual are perhaps more likely than in the past.
- Clinical trials may never be the same again!

Factors affecting trial disruption
(3) Nature of the intervention?

- The extent of the disruption depends on the type intervention.
  - Can virtual visits substitute for real visits?
  - If a trial requires multiple patient visits for assessment, even with virtual visits, delays and missing data (not at random) will be likely.
    - Be flexible (e.g., with visit “windows”)
    - Focus on the primary endpoint.

Factors affecting trial disruption
(4) How will we modify the data collection and analysis?

- Is completion of the trial feasible? Should the sample size be decreased?
- Will the primary endpoint have to change??
- What kind of sensitivity analyses will be done?

Two examples of disrupted NHLBI trials

A “good” Example: PLAN with families (Primary care pediatrics Learning Activity Nutrition)

- A diet and exercise intervention for overweight children and one overweight parent.
  - These diads randomized to counselling or usual care.
  - Treatment is 26 or more counselling sessions over 24 months.
  - Weight and height are recorded at baseline, 6, 12, 18 and 24 months.
  - Primary endpoint is change in BMI from baseline to 2 years in the child.
  - At the disruption, accrual was complete; counselling continuing.
  - Introduced virtual counselling sessions via Zoom or Webex.
  - This was easier for the subjects. Some who had not shown up for appointments participated again.
- Focus on primary endpoint: Subjects supplied with scales and height charts and they are watched while measuring.

COVID-19 related data in PLAN (1)

- COVID-19 Exposure and Family Impact Survey (from Center for Pediatric Traumatic Stress*)
- Designed to be used in ongoing and new studies where COVID-19 may influence study outcomes.
- Conceptualizes exposure to potentially traumatic aspects of COVID-19 and assesses the impact of the pandemic on the family. Should be completed by caregivers.
  - 25 yes/no questions about COVID-19 exposure
  - 12 additional questions (Likert scale) on COVID-19 Impact on family life
  - Open ended opportunity for additional comments.
- Simple scoring system.
- PLAN will collect these data once.

*https://www.healthcaretoolbox.org/tools-and-resources/covid19.html

COVID-19 related data in PLAN (2) Questions under consideration* (a work in progress)

- Have you been sick in the past 30 days?
- Seen a doctor? How long after symptoms?
- Tested for COVID-19? Tested for flu?
- Have you socialized in groups in the past 7 days?
- Starting today how long would you be willing to avoid certain activities (restaurants, socializing with people over 60, …)
- How has this affected your work?
- Knowledge questions (select all that apply): To the best of your knowledge, which of the following can protect someone from COVID-19?

*From the CDC COVID-19 Community Survey Question Bank
https://cde.nlm.nih.gov/formView?tinyId=Kcceysolt

COVID-19 related data in PLAN (3): Questions not yet considered

- Must consider how much treatment and outcome information needed; specifically if illness occurs, does it impinge on getting outcome data.
- Fortunately this is not a high risk age group, but some are low income, which has implications for risk.

A more complex example: BMT CTN

- BMT CTN is a network that conducts hematopoietic stem cell transplantation clinical trials; many trials occur simultaneously
- On March 10, 2020, accrual was put on hold (except for one aplastic anemia trial)
- Accrual and in-person visits resumed earlier this month, depending on the center and whether the patient was willing to be seen.
- Modification of forms for visits and COVID-19 infection.

BMT CTN new data form for visits

1. Did the visit occur?*(VDFOCCUR)*

1-1 - Yes 2-2 - No

2. If Yes, record visit date:*(VDFVISDT)*

(mm/dd/yyyy)

3. If Yes, select visit type:*(VDFVSTYP)*

1-1 - Clinic Visit
2-2 - Telemedicine Visit
3-3 - Phone Contact
4-4 - Clinic Visit and Telemedicine Visit
5-5 - Phone Contact and Telemedicine Visit
*Additional Options Listed Below

4. Was the visit delayed?*(VDFDELAY)*

1-1 - Yes 2-2 - No

5. If Yes, select reason:*(VDFDLYRS)*

01-1 - Patient Illness or Injury
02-2 - Patient Refusal due to COVID-19 Concerns
03-3 - Scheduling Difficulties
04-4 - Transportation Problems
05-5 - Temporarily Out of Area
*Additional Options Listed Below

Impact of COVID-19 on BMT CTN data collected

- Co-enrollment in COVID-19 clinical trials permitted.
- BMT CTN data forms are modified to collect COVID-19 data
  - Additional questions to capture COVID-19 infection prior to the start of the preparative regimen / infusion
  - Additional questions to capture COVID-19 infection after transplant
  - Treatment for COVID-19
  - Status of COVID-19 infection at (virtual) visits
  - Option for COVID-19 as both primary and contributing cause of death

Impact of COVID-19 on BMT CTN data analysis

- The primary endpoint is usually a composite, e.g. Chronic Graft Versus Host Disease/Relapse-Free Survival.
- The primary analysis will remain the same as originally planned.
- Extensive sensitivity analyses will be undertaken.
- Trials will take longer and accrual will be slowed.

Modification of Data Analysis Plan: Sensitivity analyses (SA) for the primary endpoint (1)

- SA1: Censor patients at their last assessment for those who have a missed assessment attributed to Covid-19 or for those who have a telemedicine or phone contact visit only
- SA2: Censor patients at onset of a Covid-19 infection.
- SA3: Censor patients at the earliest of the censoring times in SA1 and SA2
- SA4: Censor patients as of the start of the Covid-19 pandemic March 10, 2020. Note that this is only feasible for a trial in which most patients are in late stage of follow up or have already completed follow up.
- SA5: Adjust for the Covid-19 era (pre vs. post) as a time-dependent covariate in a Cox model, rather than censoring at the Covid-19 pandemic start, to account for potential changes in baseline hazard rates pre vs. post Covid-19.

Modification of Data Analysis Plan (2)

- These sensitivity analyses assume the censoring mechanism is independent of the primary outcome. If there are a sizable number of such censoring events and there is evidence that the censoring is not independent, consider marginal structural models with inverse probability of censoring weighting strategies. Analysis here is an open statistical question.
- The goal of the sensitivity analyses is to assess robustness with the primary analysis. The impact of various censoring schemes on the number of events and widths of the confidence intervals will need to be considered.
- No matter what one does, interpretation will be an issue.

Summary

- This unexpected interruption will affect ongoing clinical trials, less so for trials with accrual completed than for trials with accrual interrupted.
- Trial completion may well be a problem for trials in the mid-stage of accrual. Nobody knows what will happen!
- In any case, data analysis will have to be modified, leading to new and challenging statistical methodology questions.

Acknowledgments

My thinking on this subject has been greatly influenced by discussions of the BMT-CTN Statistics Group, primarily

Brent Logan

Juan (Maggie) Wu

Eric Leifer

Adam Mendizabel

And the PLAN investigators, primarily

Len Epstein

Ken Schectman

Steve Cook

Charlotte Pratt