Considerations on impact of COVID-19 on estimands in oncology clinical trials

Compiled by industry working group "Estimands in Oncology"

(Special Interest Group sponsored by PSI and EFSPI in Europe

and Scientific Working Group of the ASA Biopharmaceutical Section in US)

- Version as of April 2020, living document

- Most recent version available on tinyurl.com/oncoestimand

- Any feedback appreciated! Contact email addresses available on the above webpage.

Document intent

- This is a library of information, designed for you to pick and choose slides relevant to your particular context.
  - Overall intent: provide you with key points to consider to support discussions with your teams and potentially with Health Authorities about the impact of COVID-19 on your trial.
  - Assumes some familiarity with the estimand concept as introduced in the ICH E9 addendum.
  - We consider this a living document and anticipate updates as the drug development community learns.
- Who should use this deck?
  - Anyone who wishes to talk about the impact of COVID-19 on oncology trials.
  - May also be informative for trials in other indications.
- Who is the targeted audience?
  - Any partner who needs to assess impact of COVID-19 on an oncology clinical trial.

Coronavirus Disease 2019

COVID-19 is dramatically impacting communities and public health systems around the globe.

As of April 5th:
- >1.26 million infected
- >68k deaths
- >quarter of the world's population under lockdown
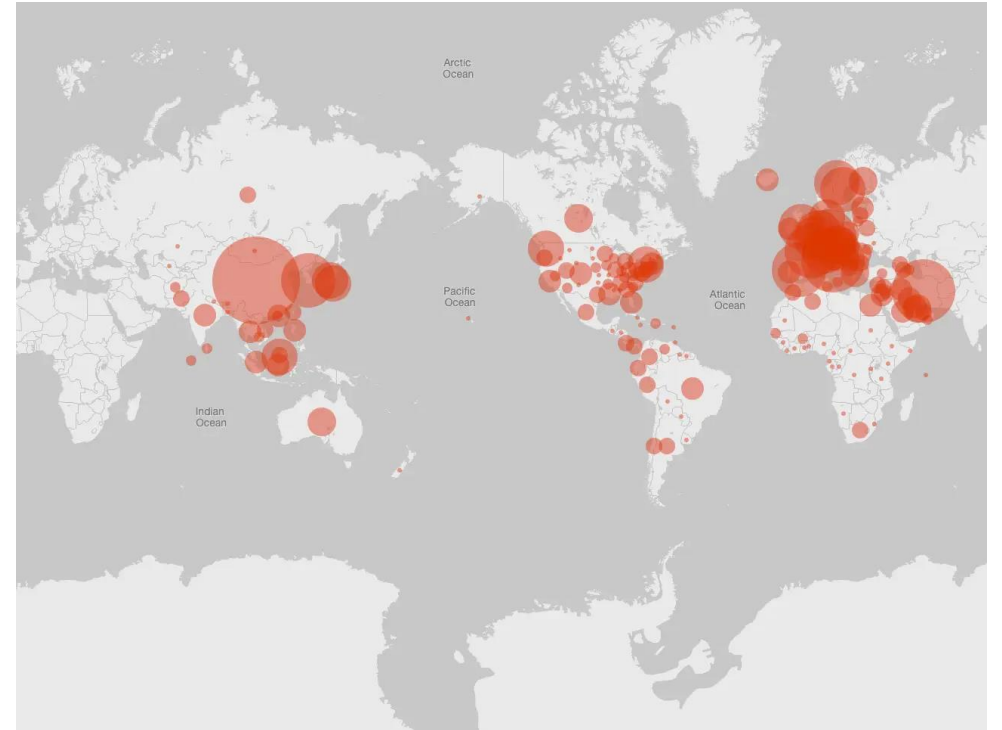
Impact on cancer patients

For cancer patients, the virus and measures to curb its spread are already impacting their disease, treatment, and monitoring.

- **Indirect**: prioritization of COVID-19 patients; overwhelmed healthcare systems; travel restrictions; oncologists are asked to weigh the risk of missing a cancer treatment or medical appointment against the possibility of exposing a patient to infection.
- **Direct**: infection; treatment for COVID-19.

Safety, conduct, and integrity of ongoing clinical trials are in jeopardy and require evaluation / action.

ELSEVIER

Annals of Oncology
Available online 26 March 2020
In Press, Journal Pre-proof ⑦

Original Article

Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China

L. Zhang [1,#], F. Zhu [2,#], L. Xie [3], C. Wang [2], J. Wang [4], R. Chen [2], P. Jia [2], H.Q. Guan [2], L. Peng [5], Y. Chen [1], P. Peng [1], P. Zhang [1], Q. Chu [1], Q. Shen [1], Y. Wang [6], S.Y. Xu [6], J.P. Zhao [6], M. Zhou [6]

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Coronavirus

Coronavirus: What People with Cancer Should Know

ON THIS PAGE

- What is coronavirus, or COVID-19?
- If I have cancer, am I at higher risk of getting or dying from COVID-19?
- If I have cancer, how can I protect myself?
- I receive cancer treatment at a medical facility. What should I do about getting treatment?
- I participate in a clinical trial at a medical facility. What should I do?
- What should I do if I have symptoms of an infection?

The estimand framework

A framework to align planning, design, conduct, analysis, and interpretation of a clinical trial.

Five attributes as described in **ICH E9 addendum**:

1. **Population** of patients targeted by the clinical question.

2. **Treatment** condition of interest.

3. **Variable** (or endpoint) to be obtained for each patient that is required to address the clinical question.

4. Handling of **other intercurrent events** (events occurring after treatment initiation that affect the interpretation/existence of measurements associated with the clinical question).

5. **Population-level summary** providing a basis for comparison between treatment conditions.

Typical objective of an oncology trial before the pandemic

The trial will compare Drug A with Standard of care in first-line follicular lymphoma patients.

The primary comparison of progression-free survival will be made regardless of whether patients discontinue treatment or receive new anti-lymphoma therapy prior to disease progression.

The primary comparison of interest is the hazard ratio of progression-free survival.

The primary trial objective is to demonstrate superiority of the experimental over the control treatment.

Problem statement

Trial Objective

↓

Estimand

↓

Main Estimator

↓

Main Estimate
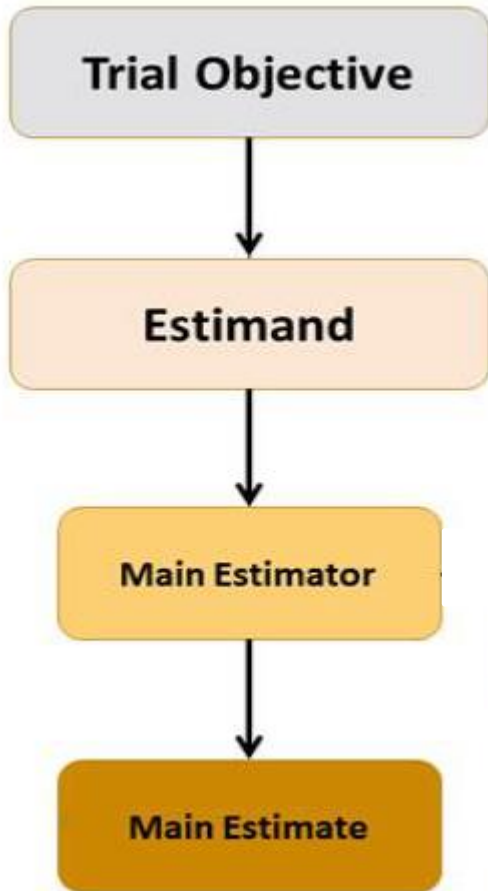
- COVID-19 pandemic causes overwhelming disruption of healthcare systems leading to inaccessability of sites, treatment interruptions and discontinuations, missed or delayed visits, use of unexpected conmeds, deaths etc.

- **Does estimate from initially planned analysis still provide the answer to the main question of interest** reflected in the trial objective/estimand in light of unforeseen COVID-19 impact?

- Will the trial results inform physician's decision in post-pandemic world (e.g. when a vaccine is available) accurately?

- There may be a **need to clarify the estimand in consistency with initial question of interest and taking into account intercurrent events due to COVID-19**
  - Clarified question of interest could be e.g.
    «**How would Drug A compare to SoC in the absence of overwhelming global disruption of healthcare systems (as is the ongoing case with COVID-19) and deaths or discontinuations due to COVID-19 infections?**"
  - **Change in estimand may** also **require change in estimator.**

Are we still estimating our target of estimation (estimand)?
Population

Population attribute: *...first-line follicular lymphoma patients.*

- We assume at some point this pandemic will be over.

- Remains the population we continue to be interested in.

Potential issue with estimator described in the protocol/SAP prior to COVID-19: **Patients in the trial not representative of the targeted population anymore?**

- Characteristics of patients recruited pre-, during, and post-pandemic might differ.

- During pandemic, enrollment may lean towards ...
    - healthier patients (able to travel, no symptoms),
    - patients with lower risk of COVID-19 (age),
    - patients with more advanced disease and poor prognosis,
    - patients in regions of lower infection rate (social distancing, quarantine measures).

- Delayed diagnosis during pandemic may result in systematic difference in patient characteristics of those enrolled post-pandemic vs pre-pandemic.

- If recruitment on-hold during pandemic: at analysis, more events from patients enrolled pre-pandemic and possibly affected by COVID-19.

Are we still estimating our target of estimation (estimand)?
Treatment

Treatment attribute: *… compare Drug A with Standard of care… regardless of any new anti-lymphoma therapies*

- Assuming at some point this pandemic will be over, we remain interested in the initially defined treatment conditions.

Potential issue with estimator described in the protocol/SAP prior to COVID-19: **received treatment and its duration in the trial not anymore representative of what would have been administered pre-pandemic and will be administered post-pandemic?**

- Treatment delays, interruptions or discontinuations for various reasons:
  - COVID-19 infection.
  - Patient's or physician's decision:
    - not to receive further anticancer treatment due to immunosuppression,
    - to skip doses or discontinue treatment avoiding travelling (e.g. if patient is in remission and maintenance therapy is stopped, which is suggested as an option in ASCO guideline).
  - Availability of oral therapies in the same indication may lead to discontinuation of IV study drugs.
  - Unexpected changes in competitive landscape (e.g. approvals of new drugs while the recruitment is on hold) may also lead to higher trial discontinuation rate than initially anticipated (in particular, more withdrawal of consent in control arm) → more missing data than anticipated.
  - Drug supply issues or other logistic reasons at sites.
- Possible impact of additional therapies used to treat COVID-19 infections or as prophylaxis on study drug effect.

Are we still estimating our target of estimation (estimand)?
Variable (endpoint)

Variable attribute: *...progression-free survival*

- we may consider an intercurrent event "death due to COVID-19" using different strategies in estimand framework, e.g.
  - Hypothetical: death due to COVID-19 not event of interest and not included in endpoint definition (e.g. estimation: censor at death due to COVID-19)
    - This would require an update of the initially defined time-to-event endpoint (e.g. to "time from randomization to progressive disease or death due to causes other than COVID-19").
  - Composite: death due to COVID-19 included in endpoint definition and counted as event.
- Considerations apply to time-to-event endpoint in general, i.e. EFS, PFS, OS.

Potential issue with estimator described in the protocol/SAP prior to COVID-19: **will the currently defined endpoint reflect the treatment effect in a post-pandemic world?**

- impacted by alternative methods for assessments (e.g. use of healthcare provider close to patient's home with other imaging device or modality possibly resulting in higher number of scans with unknown results),
- impacted by change in visit schedule or missed efficacy evaluations due to logistic issues, travel restrictions and patient's and physician's decisions,
- impacted by deaths due COVID-19,
- possibly higher proportion of "deaths due to other causes" during the pandemic, e.g. disruption of healthcare system.

Are we still estimating our target of estimation (estimand)?
other intercurrent events

Intercurrent events: *...regardless of whether patients discontinue treatment prior to disease progression*

- Possible new intercurrent events due to COVID-19 require further consideration:
  - COVID-19 infection related events:
    - COVID-19 infection.
    - Death due to COVID-19 infection.
    - Treatment interruptions or discontinuations due to infection.
    - Start of concomitant medication to treat COVID-19 possibly interfering with study drug's mechanism of action.
  - Events due to systematic disruptions of health care system
    - Treatment interruption or discontinuations due to drug supply issues, patient's or physician's decisions.
    - Logistic issues at site causing missing visits.

Potential issue with estimator described in the protocol/SAP prior to COVID-19: **all intercurrent events, whether directly or indirectly related to COVID-19, meaningfully handled with current analysis conventions to reflect the treatment effect in a post-pandemic world?**

- Follow-up data interpretable after COVID-19 infection, treatment interruptions, discontinuations or start of conmeds?
- Pre-specified analysis targeting now a different estimand than initially planned with different treatment and variable attributes?

Are we still estimating our target of estimation (estimand)?
Population-level summary

Population-level summary: *hazard ratio*
- Remains the population-level summary of interest.

Changes in estimator described in the protocol/SAP prior to COVID-19 may be **needed dependent on how intercurrent events due to COVID-19 are handled**.

Key intercurrent events due to COVID-19: COVID-19 infection

- Probability for a patient to get COVID-19 considered generally independent of randomized treatment, but some exceptions possible and clinical input important to confirm it.

- Impact depends on patient characteristics (e.g. age, severity of the disease) and the time of infection related to treatment and other trial endpoints.

- COVID-19 infection to be reported on AE CRF; if infection leads to delays/interruption in treatment and/or assessments this should also be documented.

- Valuable to distinguish between confirmed (positive test) and suspected (e.g. based on pre-defined list of symptoms in absence of performed test) COVID-19 infections for analyses, in particular due to different testing strategies between regions and considering that some patients may have been impacted before widely available testing.

- Treatment policy strategy for COVID-19 infection as intercurrent event appears reasonable, however deaths, discontinuations, interruptions and ConMeds due to COVID-19 infection should be discussed as separate intercurrent events and may be handled differently.

Key intercurrent events due to COVID-19: Death due COVID-19

- All-cause deaths usually counted as event in the PFS/EFS/OS analysis.

- If interested in the treatment effect in post-pandemic world, hypothetical strategy would be reasonable (e.g. «What would be the OS benefit in absence of COVID-19 related deaths?).

- Estimation: Clinical input required to understand whether COVID-19 related deaths could be associated with poor prognosis or treatment and to select appropriate analysis method:
  - if COVID-19 related deaths are not indicative of worse prognosis, censoring may be considered (hypothetical estimand),
  - If COVID-19 deaths potentially indicate poor prognosis (e.g. other comorbidities) or the risk of COVID-19 infection differs between two arms estimation of drug effect (probability or hazard-based) might best be done in a competing risk framework.

- Clarity in data collection about the cause of death is important.

- If the number of expected COVID-19 related deaths is likely to impact the interpretation of primary analysis, protocol amendment and HA interactions should be considered.

Key intercurrent events due to COVID-19: Treatment discontinuations, interruptions and ConMeds (1/2)

- Two types to be distinguished: due to COVID-19 infection and due to disruption of healthcare system.

- Treatment discontinuations/interruptions due to disruption of healthcare system (e.g. drug supply issues, patient's, physician's decisions, logistic issues at sites):
  - Reasons for discontinuation to be clearly documented in case of patient or physician decison (e.g. patient prefers to take available oral therapy and not to travel).
  - Potential for higher rate of such discontinuations due to pandemic.
  - In blinded trials, likely to be random and not related to treatment or disease outcomes.
  - In open-label trials patients randomized to control arm may be less willing to stay on trial.

- Treatment discontinuation, interruption or ConMeds intake due to COVID-19 infection:
  - Equal probability of COVID-19 infections between two arms may be expected in most settings. Plausibility of that assumption depends on study treatments' mechanism of action and require clinical input.
  - Discontinuations may also be associated with worse outcomes.
  - Frequency of COVID-19 infections may differ between various hematology and solid tumor indications and regions.
  - Clinical input needed to assess the impact of ConMeds on study drug efficacy and disease outcomes.

- Lack of treatment and change in treatment could impact the interpretation of planned analyses in many trials.

Key intercurrent events due to COVID-19: Treatment discontinuations, interruptions and ConMeds (2/2)

- No one size fits all approach possible to handle these intercurrent events.

- Generally, hypothetical or treatment policy strategies could be applied dependent on the impact of the intercurrent event on the interpretation of trial outcomes and follow-up data.

- Factors to be considered:
  - What is the length of the interruption and how likely is it to impact the outcomes?
  - Reasonable that trial outcomes would have been different if patient had not discontinued?
  - Clinically plausible to assume that if a patient stays in response/stable disease after discontinuing treatment and prior to start of new therapy, he would have also not have progressed/died staying on-treatment?
  - Discontinuation/interruption possibly related to disease or treatment? Indicative of worse prognosis?
    - Death (not necessarily due to COVID-19 infection) observed shortly after discontinuation would have likely occurred even if patient had continued treatment?
  - Did patient receive ConMeds to treat COVID-19 and could they impact the outcomes and study drug's efficacy? (possibly even prohibited per protocol?)
  - If treatment policy is used for discontinuation, should hypothetical strategy be applied to start of new therapy after COVID-19 discontinuation even if new therapies after discontinuation for other reasons are handled with treatment policy strategy?

Missing data due to COVID-19

- Potentially more withdrawals from trials.

- More missing imaging assessments expected due to travel restrictions and disruption of healthcare system:

  - multiple missing scans before death/progression,

  - confirmation of response possibly missing,

  - partial / complete responses not captured before later progression.

- Where feasible capture reasons for missed assessments.

- Missing data strategies complement handling of intercurrent events:

  - e.g. if we are interested in the treatment effect if patients had not discontinued treatment due to COVID-19 and it is clinically plausible to assume that post-discontinuation data (if fully available) reflects patient's journey if he had continued treatment, treatment policy strategy and follow-up data could be used;

  - however, for patients with completely missing efficacy assessments due to COVID-19 or those with death observed after multiple missing scans censoring at last assessment may be appropriate method to handle missing data.

Additional considerations for studies with ORR endpoint

- ORR generally likely to be less affected:
  - not impacted if response (and confirmation as needed) already observed,
  - if responses durable, missing first scans may be less problematic as response can still be observed at later timepoint,
  - however, deaths due COVID-19 prior to observed response would be considered non-responder (as all other early deaths); use of hypothetical strategy may be considered.

- DoR potentially more affected:
  - shorter duration of response due to lower exposure caused by interruptions and discontinuations due to COVID-19,
  - use of hypothetical vs treatment policy strategy for COVID-19 related treatment discontinuation requires clinical input:
    - responses may last far beyond treatment discontinuation,
    - early relapse after discontinuation may indicate that the patient would have relapsed soon after discontinuation,
  - missing assessments impact observed DoR, although censoring at last available assessment may be reasonable in many cases.

- Need to be careful comparing with pre-pandemic or post-pandemic external controls or in Bayesian designs (borrowing across cohorts in platform trials, use of prior from pre-pandemic data).

- Total sample size in single arm trials usually relatively small and summaries of patient characteristics and outcomes pre/during/post cutoff may be difficult to interpret.

Additional considerations for trials with sequences of interventions

- In trials with multiple stages of treatment (e.g., induction, consolidation and maintenance), treatment for next stage often depends on the outcome of treatment from previous stage.
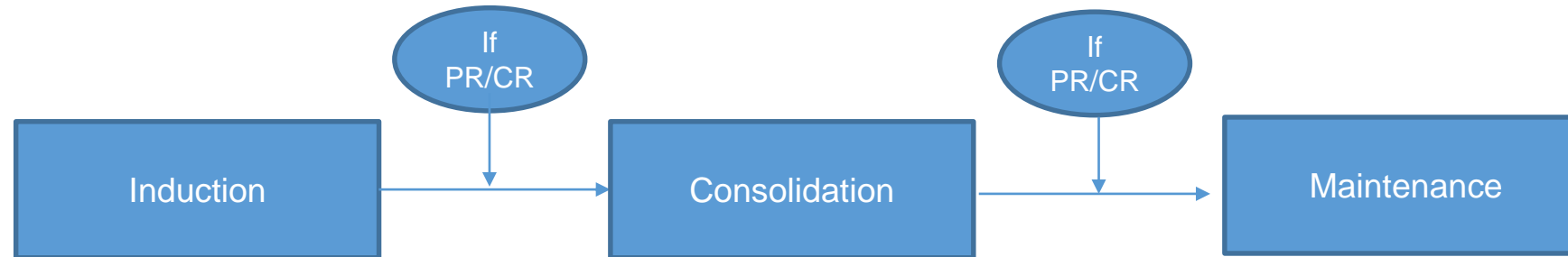
- Patients may not be willing to travel to receive the next stage treatment as they are already in PR/CR, in particular, in the maintenance phase.

- The length of the treatment sequence and that later stages are conditional on early outcomes increase the probability for intercurrent events due to COVID-19 to occur.

- High risk that patients do not complete the planned sequence of interventions and the observed outcome will not reflect what would have been observed in pre- or post-pandemic world.

- Similar issues may be observed in neoadjuvant/adjuvant trials.

Additional considerations for trials with one time treatments such as transplant or CAR-T therapies

- Access to transplant or CAR-T might be restricted due to COVID-19 infections of patients or donors, logistical reasons or travel restrictions.

- Treatment typically consists of a sequence (chemotherapy followed by transplant or bidging therapy followed by CAR-T therapy).

What can happen because of COVID-19 pandemic?	Impact on patient compared to pre- or post-pandemic world	What does it mean?
Logistic issues at sites (e.g. ICU bed availability)	• CAR-T infusion or transplant delayed • Longer pre-treatment with bridging/chemotherapy • CAR-T infusion or transplant not received due to delay (died or not anymore eligible due to worsen status)	• Deviation from planned treatment schedule • Follow-up data may not represent patient's journey on the planned treatment in pre-pandemic world • Initially planned analysis may not anymore target pre-pandemic estimand
Manufacturing constraints for CAR-T (e.g. flight cancellation)		
Physician decision to delay transplant/CAR-T in responders after chemotherapy		
COVID-19 infection prior to CAR-T or transplant		

Considerations for data collection:
- If treatment delayed – will the next per-protocol scheduled tumor assessment be informative or is a change in schedule needed for such patients?
- Initially planned date of transplant/CAR-T infusion may be required for some analyses.

Considerations for analysis:
- If treatment received with delay, but within reasonable time, follow-up data still likely to reflect patient's journey in pre-pandemic world and could be used in the analysis?
- If treatment not received – follow-up data still reflects patient's pre-pandemic journey? Early death during the delay likely would have happened even if infusion/transplant received? If follow-up data not representative, censoring or possibly excluding patients who did not receive treatment sequence due to COVID-19 may be considered.
- Longer pre-treatment with bridging/chemotherapy can result in greater delayed effect and loss of power.

Analysis considerations

- Multistate models could be used to investigate the impact of clinical hold:

  - Nießl, A, Beyersmann, J, Loos, A. Multistate modeling of clinical hold in randomized clinical trials. *Pharmaceutical Statistics*. 2019; 1– 14. https://doi.org/10.1002/pst.1989

- Potential approaches (focusing on the implications of population and intercurrent events on summary attribute):

  - Competing risk analyses.

  - Pre- and post-pandemic only analysis (remove patients ongoing or affected in pandemic and replace post-pandemic with patients meeting I/E criteria).

  - Cox model with a time-varying covariate for infection status (Y/N) or pre-, during-, and post- pandemic period.

  - Weighting approaches (IPCW), RPSFT.

- Check balance of potential issues (intercurrent events and missing data) between treatment groups and evaluate potential power loss and attenuation of treatment effect (e.g. due to increased mortality in both arms or lack of treatment).

- Review of proportion of censored observations, overall follow-up time and reasons for censoring necessary for the evaluation of drop-out rate, informative censoring and their impact on the outcome.

- Weigh the pro/cons for early read-out (e.g. if you already have 95% of targeted events pre-pandemic), delaying the trial readout or increasing sample size and/or number of events or duration of follow-up.

Further considerations (1/2)

- Safety analyses: impact of COVID-19 to be carefully assessed to ensure that safety analyses reflect the safety profile of the drug:
  - overestimation of infection rate/AEs leading to death possible and more profound in single-arm trials in absence of randomization,
  - in some cases it may be difficult to elucidate contribution of study treatment vs. COVID-19 to specific Aes,
  - proper data collection in CRF important.

- PRO endpoints directly affected by COVID-19 and require pre-, during- and post-COVID-19 analyses.

- Non-inferiority trials: some COVID-19 related intercurrent events may result in type I error increase if not carefully taken into account in the estimand and analysis.

- «Affected data» and pre/during/post-pandemic periods must be carefully defined on patient and endpoint level, in particular in open-label trials:
  - e.g. for some patients response observed pre-pandemic, but DoR/PFS/OS may still be affected,
  - collected trial data may not be sufficient to determine affected periods in objective way, alternatives such as e.g. first COVID-19 case in patient's country could be considered.

Further considerations (2/2)

- Implementation of changes to study design/endpoints requires careful discussion not only in open-label studies, but also in double-blind trials (e.g. unblinded DMCs may not be the best way).

- Further discussion about the use of principal stratum in some situations (e.g. «What would be the effect in patients who would have never get COVID-19 infection?», in particular if the likelihood of infection differs between two arms), warranted, although estimation may be challenging.

- Group-sequential or adaptive clinical trials with interim analyses:
  - iDMC has to understand and appreciate all the above implications of COVID-19.
  - Population difference over time is a particular issue for conditional power calculation and decisions on efficacy in Phase 3, which rely on homogeneity.

- For certain indications, post-pandemic world might forever be different, e.g. impact of COVID-19 presence in humanity on lung diseases (need to collect it as baseline characteristic for future trials?).

- Many considerations could also be useful in future situations with other (potentially "only" local) disruptions of healthcare systems (Examples: Fukushima accident in Japan).

- Rapid response illustrates usefulness of purpose-built-networks such as the industry WG Estimands in Oncology.

References and useful links

- ICH E9 addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf

- FDA guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic https://www.fda.gov/media/136238/download

- EMA guidance on the Management of Clinical Trials during COVID-19 Pandemic and Points to consider on implications on methodological aspects https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical_en.pdf

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- L.Zhang et al. Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China, Annals of Oncology, 2020 https://doi.org/10.1016/j.annonc.2020.03.296

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Back-up

Examples of tables that may help to structure team discussions

Excerpts from two possible tables for illustration purpose

Clinical event	Reason	Impact on estimand	Potential strategy	Implementation and Interpretation of strategy	Impact on data collection
Death	COVID-19	Intercurrent event	Hypothetical	Censor at death due to COVID-19. Estimate treatment effect in a world where COVID-19 would not happen.	none
			Composite	Count death irrespective of it potentially being treatment / disease unrelated.	none
Administration of antiviral concomitant treatment	COVID-19 unproven and/or prophylactic	Intercurrent event	Hypothetical	Impute using data from "similar" patients who did not get such treatment	Collect details of such treatment
			Treatment policy	Ignore such treatment for computation of endpoint	Collect data after ConMeds
Withdrawal from trial	Any	missing data	N/A	Check the reason for missing data and whether preceding intercurrent event lead to withdrawal	

Issues or Impact on study conduct	Impact compared to pre- or post-pandemic world	Proposed data collection	Key statistical issues and impact on data Interpretation/trial integrity	Possible ways to address hypothetical question: What if COVID-19 had not occurred
Missed/Delayed assessments	Higher rate of missed/delayed assessments during the pandemic	Where feasible capture reasons for missed/delayed assessments	Depends on the amount of missing data or the length of the delay in capturing and whether or not other trial outcomes have already been observed	Consider if censoring prior to pandemic is an appropriate approach (e.g. if more than x missed assessments followed by a PD event consider censoring). Examine reasons/amount of censoring or missed assessments across arms to assess bias
Treatment delayed or interrupted	High rate of treatment interruptions or delays during the pandemic	Report reason for treatment dealy /interruption if related to COVID-19	Extended delay/interruption could impact efficacy outcomes.	If patient still receives therapy within reasonable time, consider data as interpretable? If not, or patient even dies during the delay, censor, but do sensitivity? Consider exclude patients not receiving treatment