ANSWERING OLD QUESTIONS WITH NEW TOOLS

APPLICATION OF THE ICH E9 ADDENDUM IN ONCOLOGY

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Genentech
A Member of the Roche Group

"The intellectual illness of clinical drug evaluation that I have discussed here can be cured, and it will be cured when we restore intellectual primacy to the questions we ask, not the methods by which we answer them."

– Lew Sheiner, American Clinical Pharmacologist

Agenda

1. ICH E9(R1) Addendum
2. Application to duration of response and time to response
3. Other applications in oncology
    - CAR-T
    - Treatment switching
    - Covid-19/Ukraine crisis
4. Impact and conclusions

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Co-authors (Section 2):

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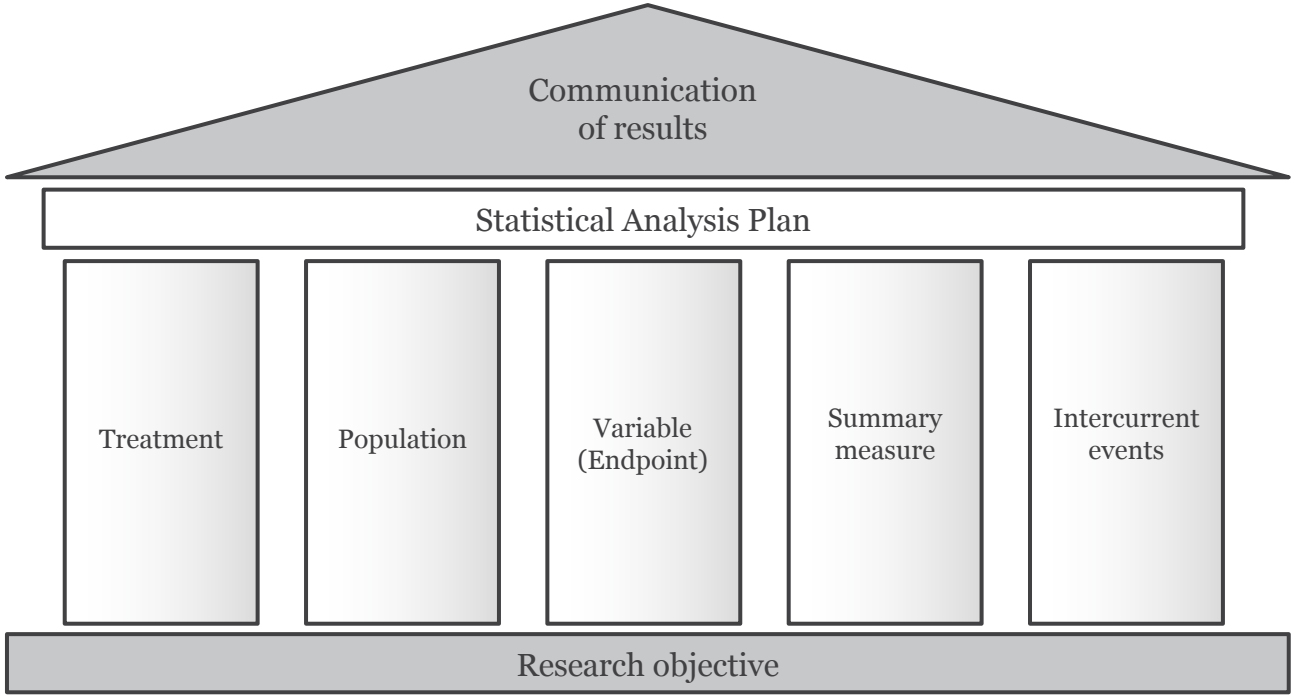
ICH E9(R1) ADDENDUM

The estimand framework

An estimand is a **detailed description of the treatment effect**, estimated to address a scientific question of interest.

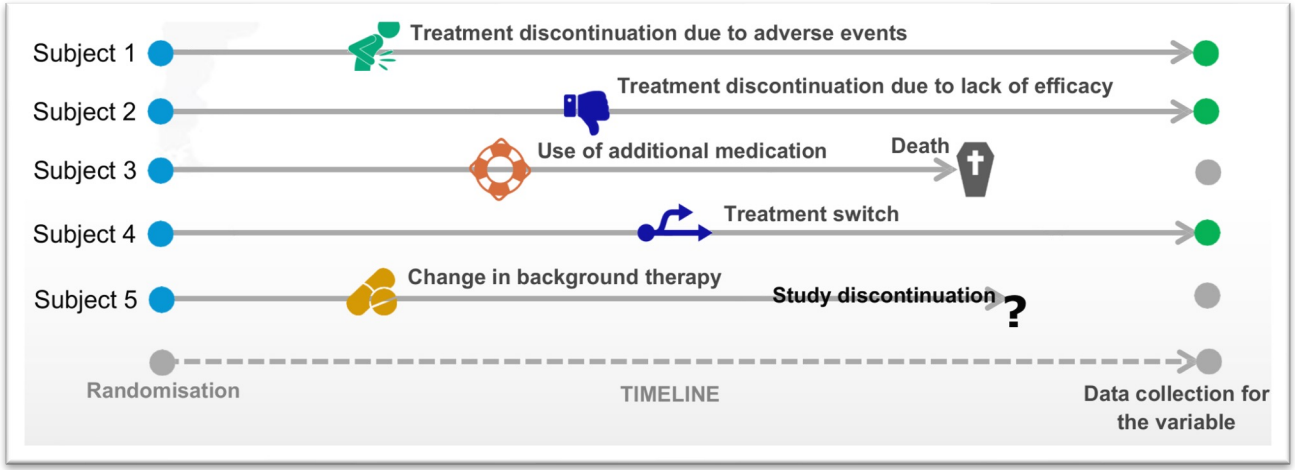
Estimands ensure that **study objectives** align with **design, conduct, analysis, and interpretation** of the trial.



Fiero et al. (2020) The Lancet Oncology

Intercurrent events (ICEs)

Intercurrent events are events that occur after treatment initiation and either preclude observation of the endpoint or affect its interpretation.



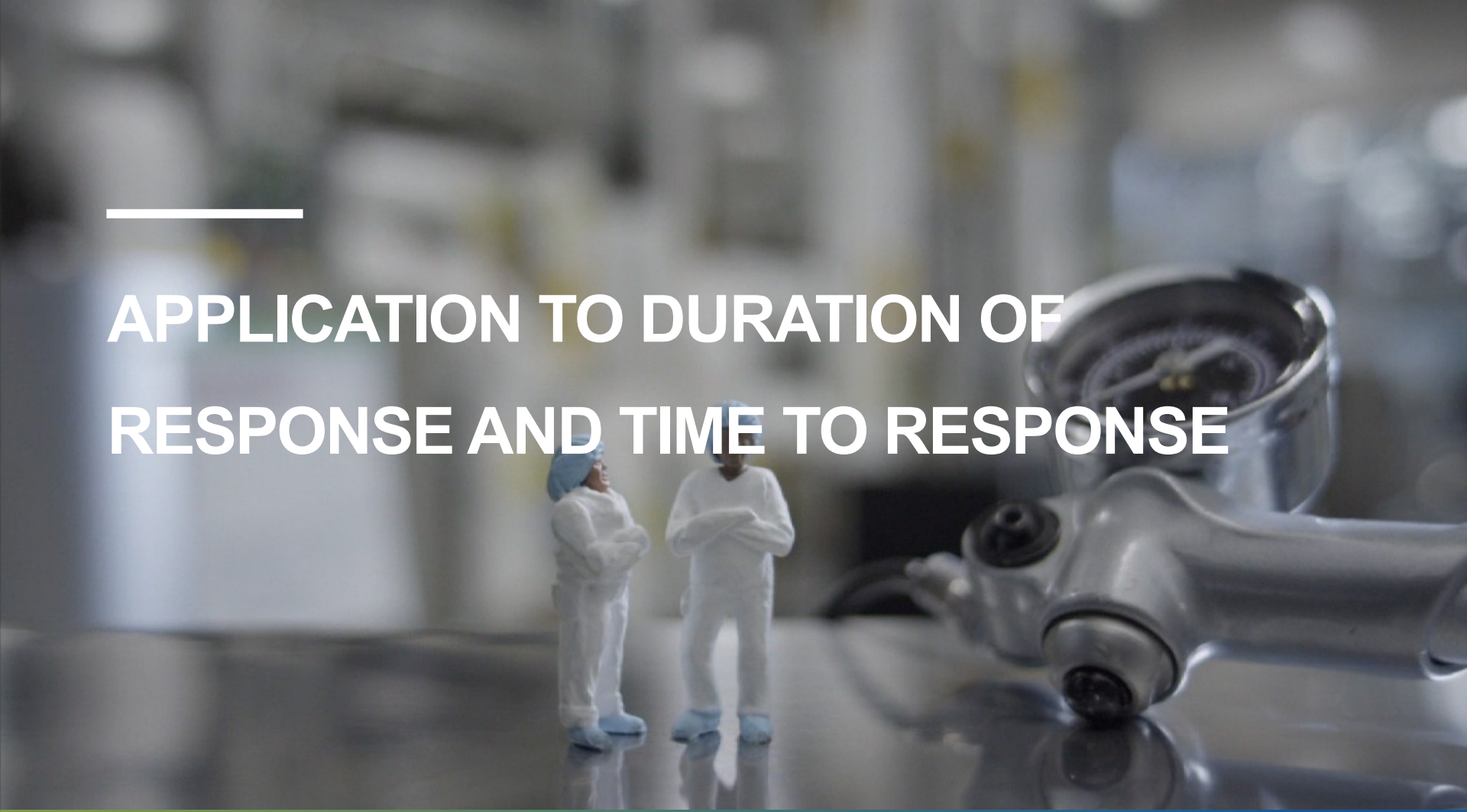
Strategies for addressing ICEs

A strategy is chosen for each ICE to **reflect the scientific question of interest**. Different strategies can be used for different intercurrent events:

1. **Treatment policy**: occurrence of ICE is irrelevant
2. **Hypothetical**: a hypothetical scenario is envisaged in which the ICE would not occur
3. **Composite**: occurrence of ICE is taken to be a component of the variable
4. **While-on-treatment**: variable outcome prior to occurrence of ICE is of interest
5. **Principal stratum**: defined by a subject's potential ICE on either or both treatment arms
6. **Treatment**: occurrence of ICE is taken to be a part of the treatment

The relevance of each strategy will depend on the **therapeutic and experimental context**.

Not all strategies will be equally acceptable to different stakeholders!

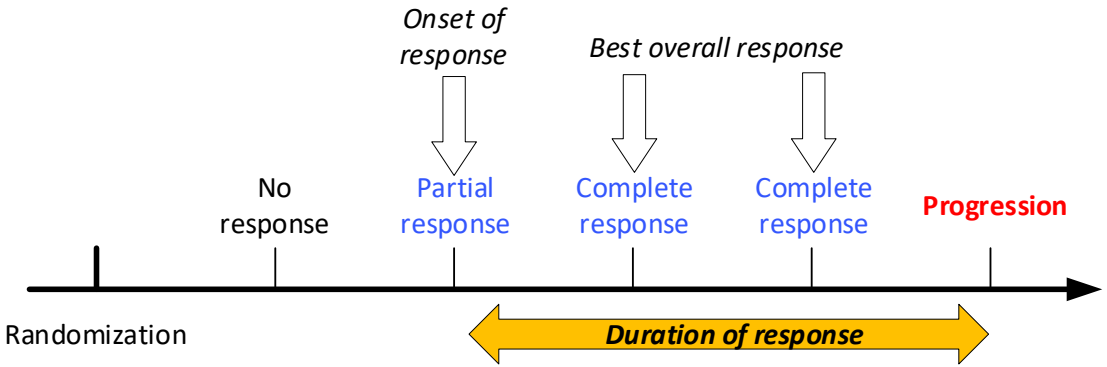


APPLICATION TO DURATION OF RESPONSE AND TIME TO RESPONSE

Early-stage oncology clinical trials

Typical setting:

- Single-arm or randomized
- Treatment effect is assessed based on response to therapy
  - Overall response rate (ORR)
  - Duration of response (DOR)
  - Time to response (TTR)



Old questions, New tools: Although DOR and TTR are frequently considered, they are oftentimes misused or misinterpreted. The ICH E9(R1) estimand framework can help investigators to identify and communicate what it is that they wish to estimate.

Duration of response

Traditional estimand

"Among responders, what is the median time from response to progression or death, regardless of treatment discontinuation but assuming absence of subsequent therapy?"

Treatment	Treatment condition of interest (and comparator as appropriate)
Population	Patients who meet the I/E criteria and who respond to treatment
Endpoint	Time from response to progression or death
Summary measure	Median
Intercurrent events	• Treatment discontinuation: "treatment policy" • Subsequent antineoplastic therapy: **"hypothetical strategy"**

Alternative estimand #1

"Among responders, what is the median time from response to progression, death or subsequent therapy, regardless of treatment discontinuation?"

Treatment	Treatment condition of interest (and comparator as appropriate)
Population	Patients who meet the I/E criteria and who respond to treatment
Endpoint	Time from response to progression or death
Summary measure	Median
Intercurrent events	• Treatment discontinuation: "treatment policy" • Subsequent antineoplastic therapy: **"composite strategy"**

Duration of response

Traditional estimand

"Among responders, what is the median time from response to progression or death, regardless of treatment discontinuation but assuming absence of subsequent therapy?"

Treatment	Treatment condition of interest (and comparator as appropriate)
Population	Patients who meet the I/E criteria and who respond to treatment
Endpoint	Time from response to progression or death
Summary measure	Median
Intercurrent events	• Treatment discontinuation: "treatment policy" • Subsequent antineoplastic therapy: "hypothetical strategy"

Alternative estimand #2

"What is the expected time in response, regardless of treatment discontinuation but assuming absence of subsequent antineoplastic therapy?"

Treatment	Treatment condition of interest (and comparator as appropriate)
Population	Patients who meet the I/E criteria ~~and who respond to treatment~~
Endpoint	**Time in response (0 for non-responders)**
Summary measure	**Expected value**
Intercurrent events	• Treatment discontinuation: "treatment policy" • Subsequent antineoplastic therapy: "hypothetical strategy"

Time to response

Traditional estimand

"Among responders, what is the median time to response, regardless of treatment discontinuation but assuming absence of subsequent therapy?"

Treatment	Treatment condition of interest (and comparator as appropriate)
Population	Patients who meet the I/E criteria and who respond to treatment
Endpoint	Time from start of therapy to onset of response
Summary measure	Median
Intercurrent events	• Treatment discontinuation: "treatment policy" • Subsequent antineoplastic therapy: "hypothetical strategy"

Alternative estimand #1

"Among responders, what is the median time to response, regardless of treatment discontinuation or subsequent therapy?"

Treatment	Treatment condition of interest (and comparator as appropriate)
Population	Patients who meet the I/E criteria and who respond to treatment
Endpoint	Time from start of therapy to onset of response
Summary measure	Median
Intercurrent events	• Treatment discontinuation: "treatment policy" • Subsequent antineoplastic therapy: **"treatment policy"**

Time to response

Traditional estimand

"Among responders, what is the median time to response, regardless of treatment discontinuation but assuming absence of subsequent therapy?"

Treatment	Treatment condition of interest (and comparator as appropriate)
Population	Patients who meet the I/E criteria and who respond to treatment
Endpoint	Time from start of therapy to onset of response
Summary measure	Median
Intercurrent events	• Treatment discontinuation: "treatment policy" • Subsequent antineoplastic therapy: "hypothetical strategy"

Alternative estimand #2

Treatment	Treatment condition of interest (and comparator as appropriate)
Population	Patients who meet the I/E criteria ~~and who respond to treatment~~
Endpoint	Time from start of therapy to onset of response **(max. follow-up time for patients who die or progress before response, censor other non-responders at last assessment)**
Summary measure	Median
Intercurrent events	• Treatment discontinuation: "treatment policy" • Subsequent antineoplastic therapy: "hypothetical strategy"

Time to response

Traditional estimand

"Among responders, what is the median time to response, regardless of treatment discontinuation but assuming absence of subsequent therapy?"

Treatment	Treatment condition of interest (and comparator as appropriate)
Population	Patients who meet the I/E criteria and who respond to treatment
Endpoint	Time from start of therapy to onset of response
Summary measure	Median
Intercurrent events	• Treatment discontinuation: "treatment policy" • Subsequent antineoplastic therapy: "hypothetical strategy"

Alternative estimand #3

"What is the proportion of patients who respond within *t* months, regardless of treatment discontinuation but assuming absence of subsequent therapy?"

Treatment	Treatment condition of interest (and comparator as appropriate)
Population	Patients who meet the I/E criteria ~~and who respond to treatment~~
Endpoint	**Response within *t* months (yes or no)**
Summary measure	**Proportion**
Intercurrent events	• Treatment discontinuation: "treatment policy" • Subsequent antineoplastic therapy: "hypothetical strategy"

Takeaways

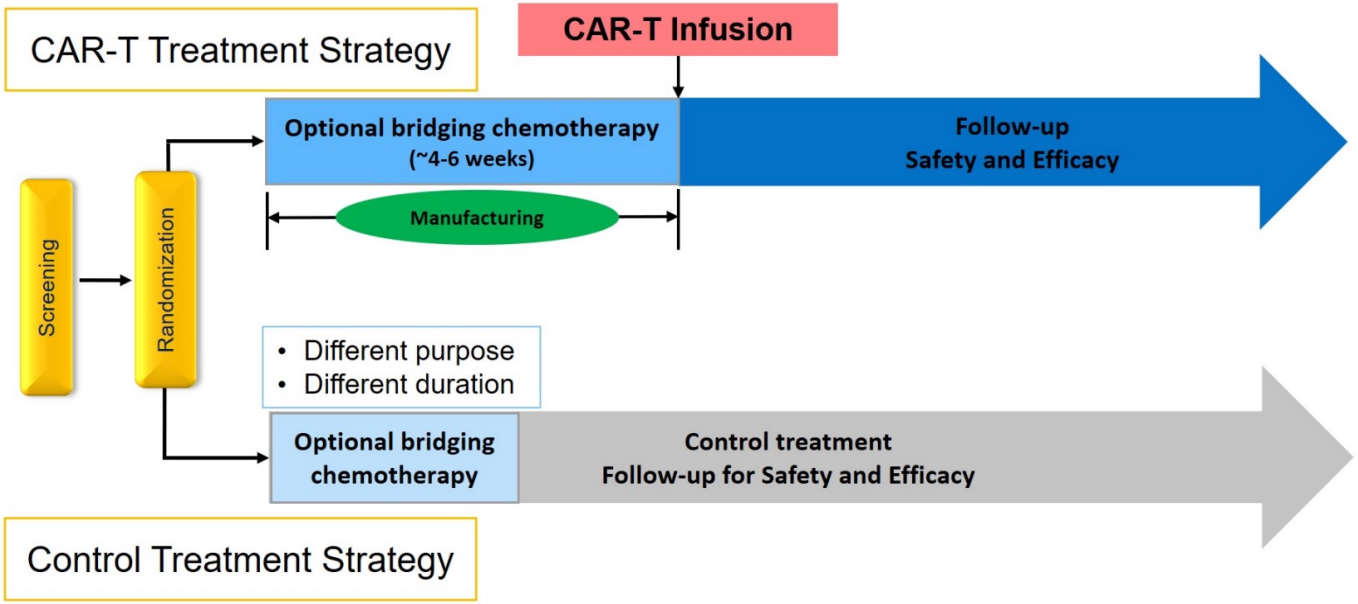
- Although DOR and TTR are frequently reported, study protocols, publications, etc. often do not describe the estimand (target of estimation). Different estimands can address very different clinical questions. Thus, **estimands should be described to facilitate proper interpretations**.

- We support the current practice of presenting ORR, DOR and TTR (among responders) together, i.e. there is no clinically meaningful interpretation of (conditional) DOR and TTR if not presented together with ORR.

- **Comparison of DOR between treatment groups should take ORR into account**. There are valid estimands available which integrate both aspects of response and duration. Likewise for TTR.
    - Time in response (EMA, 2017)
    - Response within *t* months
    - Being in response at *t* months (Ellis, 2008; Garnett, 2013)
    - Overall survival (OS)
    - Progression free survival (PFS)
    - Event-free survival (EFS)

OTHER APPLICATIONS IN ONCOLOGY

CAR-T example



Primary scientific question: overall survival (OS) comparison of entire sequence of interventions

FDA Comment on the study protocol

Subjects in the CAR-T arm may receive extensive bridging chemotherapy while awaiting CAR-T manufacture, and some, especially those experiencing extended delays in product manufacture, could achieve a CR/CRi [...] status in response to aggressive bridging chemotherapy even before initiation of CAR-T treatment. Since these responses cannot be directly attributed to CAR-T treatment, the statistical assessment plan should prospectively create rules for appropriately censoring CR [...] subjects.

FDA proposal for supplementary EFS analysis:

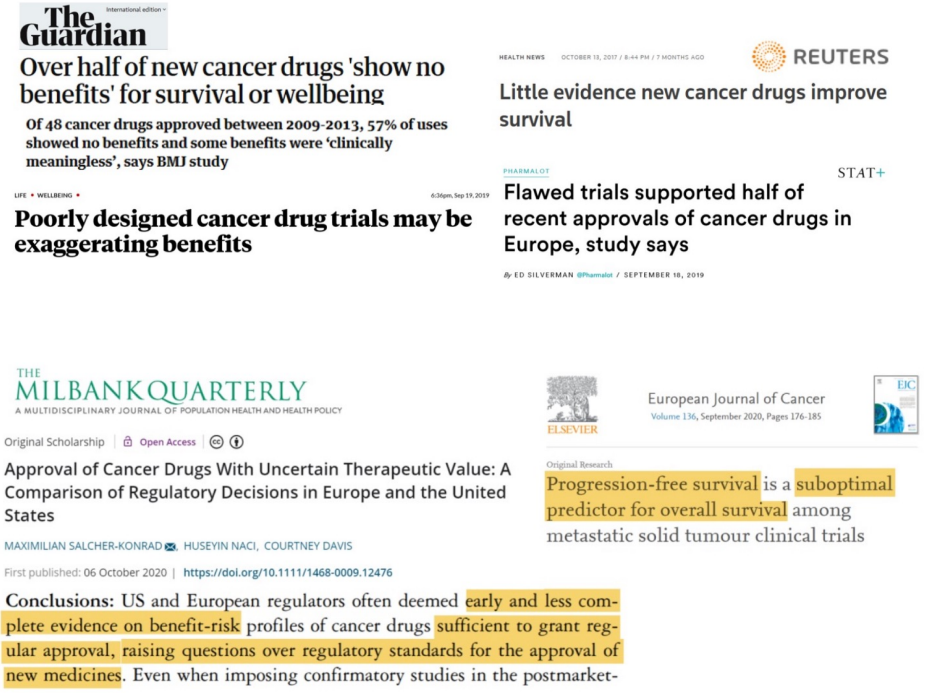
- **Censor** patients who respond to bridging chemotherapy in CAR-T arm
- Censoring targets a **hypothetical scenario** in which no patient would respond to bridging chemotherapy in CAR-T arm
- Is this estimand relevant for patients, physicians, and regulators?

Sponsor counter-proposal:

- A **principal stratum estimand** may better address FDA's actual question of interest
- "Effect in patients who would not respond to bridging chemotherapy if they were given bridging chemotherapy"
- FDA agreed

Treatment switching

- Patients are increasingly switching to subsequent antineoplastic therapy after disease progression or end of treatment (EOT).
- **Treatment policy estimand** compares two treatments regardless of whether or not patients receive subsequent therapy. Is this always clinically relevant?
- **Hypothetical estimand** considers a world in which subsequent therapy is not available. Could this also be relevant?



The Guardian

Over half of new cancer drugs 'show no benefits' for survival or wellbeing

Of 48 cancer drugs approved between 2009-2013, 57% of uses showed no benefits and some benefits were 'clinically meaningless', says BMJ study

Poorly designed cancer drug trials may be exaggerating benefits

REUTERS

Little evidence new cancer drugs improve survival

STAT+

Flawed trials supported half of recent approvals of cancer drugs in Europe, study says

By ED SILVERMAN @Pharmalot / SEPTEMBER 18, 2019

THE MILBANK QUARTERLY

A MULTIDISCIPLINARY JOURNAL OF POPULATION HEALTH AND HEALTH POLICY

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Approval of Cancer Drugs With Uncertain Therapeutic Value: A Comparison of Regulatory Decisions in Europe and the United States

MAXIMILIAN SALCHER-KONRAD, HUSEYIN NACI, COURTNEY DAVIS

First published: 06 October 2020 | https://doi.org/10.1111/1468-0009.12476

Conclusions: US and European regulators often deemed early and less complete evidence on benefit-risk profiles of cancer drugs sufficient to grant regular approval, raising questions over regulatory standards for the approval of new medicines. Even when imposing confirmatory studies in the postmarket-

ELSEVIER

European Journal of Cancer

Volume 136, September 2020, Pages 176-185

Original Research

Progression-free survival is a suboptimal predictor for overall survival among metastatic solid tumour clinical trials

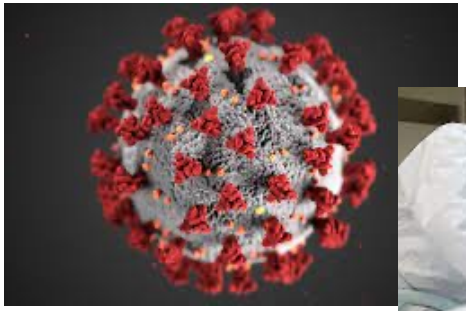
Covid-19 Pandemic and Ukraine-Russia Crisis

The addendum has also been a useful tool for

- assessing the risks posed by **current events** on the interpretability of trial results, and
- proposing measures to curb those risks.

Example of impacts:

- Delayed or missing assessments
- Treatment interruption or discontinuation
- Patients receive non-protocol therapy
- Death or hospitalization due to current event
- Inability to perform source data verification
- And more …



CONCLUSION

Impact of the ICH E9(R1) Addendum

Aligning stakeholder's expectations for target treatment effect **upfront** has potential to give:

- Increased **transparency** and **clarity** with respect to assumptions, data analysis, and inference
- Clarity about **added value** of drugs: **meaningful** descriptions of treatment effects for licensing and prescribing decisions
- Clinical trials with designs, conduct and analysis that are **aligned to agreed objectives**
- Clear language to describe and discuss different estimands required by different stakeholders
- More **predictable** regulatory assessment procedures

"Design trumps analysis."

– Don Rubin, American Statistician

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Doing now what patients need next