Statistical and Executional Considerations for Trials Impacted by COVID-19 Pandemic

BBSW 2020

August 13th, 2020

Outline

- Introduction
- Efficacy Analyses: Using Estimand Framework to Handle Impact of COVID-19
  - Marcel Wolbers, Ph.D., Expert Statistical Scientist, Roche/Genentech
  - Chin-Yu Lin, Ph.D., Director of Biostatistics, Roche/Genentech
- Tools to Assess Impact of COVID-19 on Data Integrity and Interpretability
  - Zoe Zhang, Ph.D., Principal Statistical Scientist, Roche/Genentech
  - Chin-Yu Lin, Ph.D., Director of Biostatistics, Roche/Genentech
- Summary

Introduction

US clinical trial sites are most affected due to the Covid-19 pandemic

By GlobalData Healthcare

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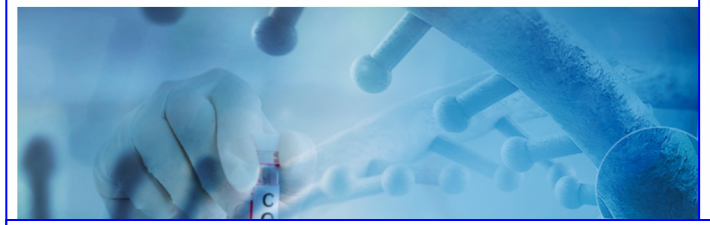

COVID-19 And Its Impact On Clinical Trials

By Ed Miseta, Chief Editor, Clinical Leader
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Debora Araujo, founder and CEO of ClinBiz, recently hosted a live online discussion on the COVID-19 pandemic and the impact it will have on clinical trials. Participating with Araujo on the call was Rosalie Filling, VP of R&D operations at Endo Pharmaceuticals, Michael Young, principal of biomedwoRx: Life Sciences Consulting, Terry Walsh, owner of Walsh Pharma Consulting, Jeff Kingsley, founder and CEO of IACT Health, and Julie Daves, senior director of clinical operations & outsourcing at miRagen Therapeutics. The purpose of the call was to share knowledge of how the pandemic might impact clinical trials and what sponsor companies can do to adapt.

The first topic the panel tackled was monitoring. The monitoring of patients is perhaps the greatest ongoing challenge sponsors face during the pandemic. Filling noted the challenge for everyone involved with clinical trials will be providing efficient monitoring and oversight for the studies while also keeping patients safe. That will involve discovering new ways to perform those functions.

Impact of Covid-19 pandemic on clinical trials evaluating various neurology indications

By GlobalData Healthcare

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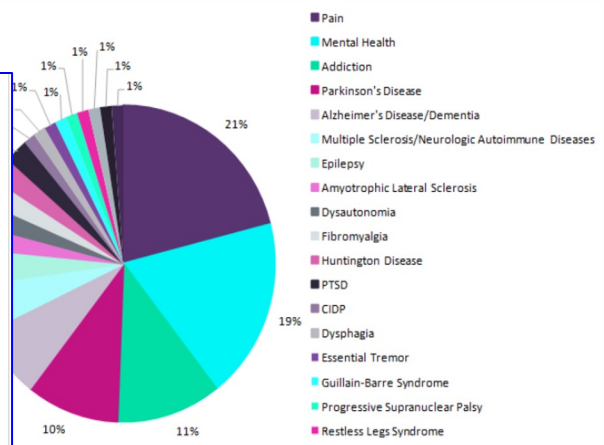

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FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency

Guidance for Industry, Investigators, and Institutional Review Boards

March 2020

Updated on July 2, 2020

may be submitted at any time for Agency consideration. Submit written comments to the nagement Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. ville, MD 20852. Submit electronic comments to https://www.regulations.gov. All hould be identified with the docket number listed in the notice of availability that the *Federal Register*.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

HMA
Heads of Medicines Agencies

GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC

Version 3

28/04/2020

Key changes from v2 (27-03-2020): distributor to trial participant IMP shipment, monitoring, remote source data verification and communication with authorities

Roche

DEPARTMENT OF HEALTH & HUMAN SERVICES • USA
FDA

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Contains Nonbinding Recommendations

Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency

Guidance for Industry

June 2020

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

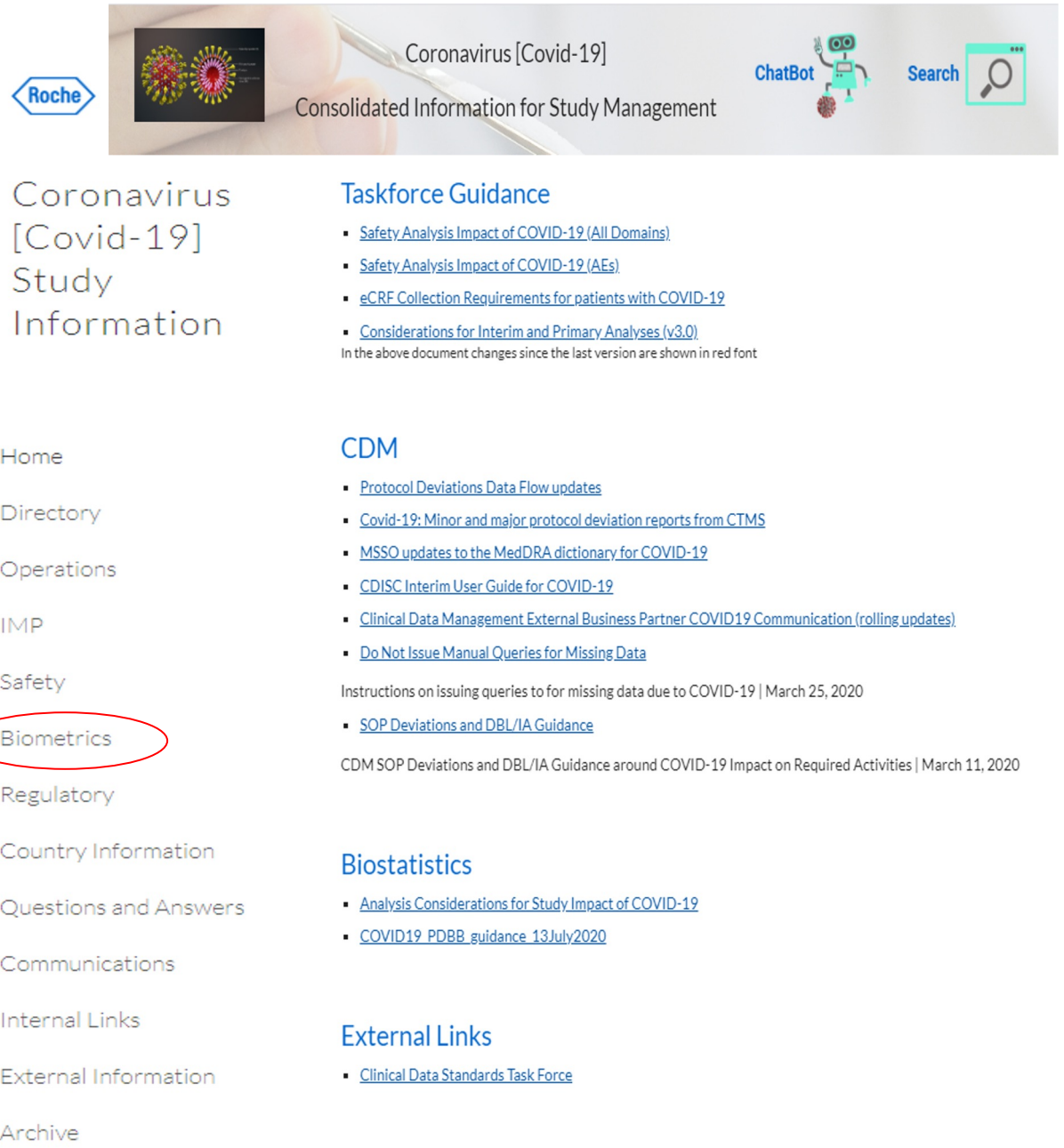
1 25 March 2020
2 EMA/158330/2020
3 Committee for Human Medicinal Products (CHMP)

4 Points to consider on implications of Coronavirus disease
5 (COVID-19) on methodological aspects of ongoing clinical
6 trials
7 Draft
8

9

Roche/Genentech Internal Efforts

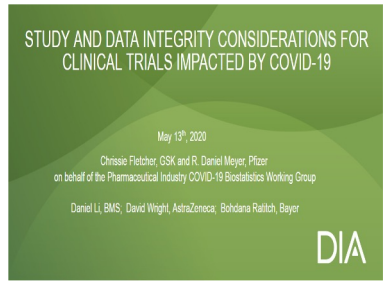
- Roche Internal Guidance
  - Dedicated COVID-19 taskforce
  - Cross-functional teams on study conduct, data handling, and documentation
  - Specific guidance on statistics and analysis considerations
- Objectives:
  - Ensure patients safety
  - Not compromise integrity and interpretability of clinical trials

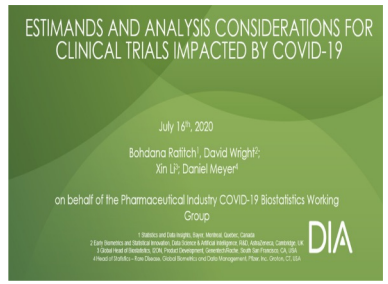


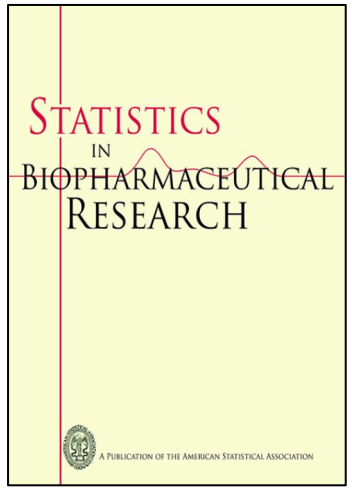
Pharmaceutical Industry COVID-19 Biostatistics Working Group

Institution	Member	Institution	Member
abbvie	Jyotirmoy Dey	GlaxoSmithKline	Christine Fletcher
	Stefan Englert	janssen	Norm Bohidar
AMGEN	Thomas Liu	Lundbeck	Ingrid Sofie Harbo
AstraZeneca	David Wright	MERCK	Yue Shentu
BAYER	Olga Marchenko	Pfizer	R. Daniel Meyer
	Bohdana Ratitch	Roche Genentech A Member of the Roche Group	Xin Li
Bristol Myers Squibb™	Daniel Li		Marcel Wolbers
	Ming Zhou	SANOFI	Peng-Liang Zhao
Lilly	Wei Shen		Hui Quan
GILEAD	Gerald Crans	Takeda	Michael Hale

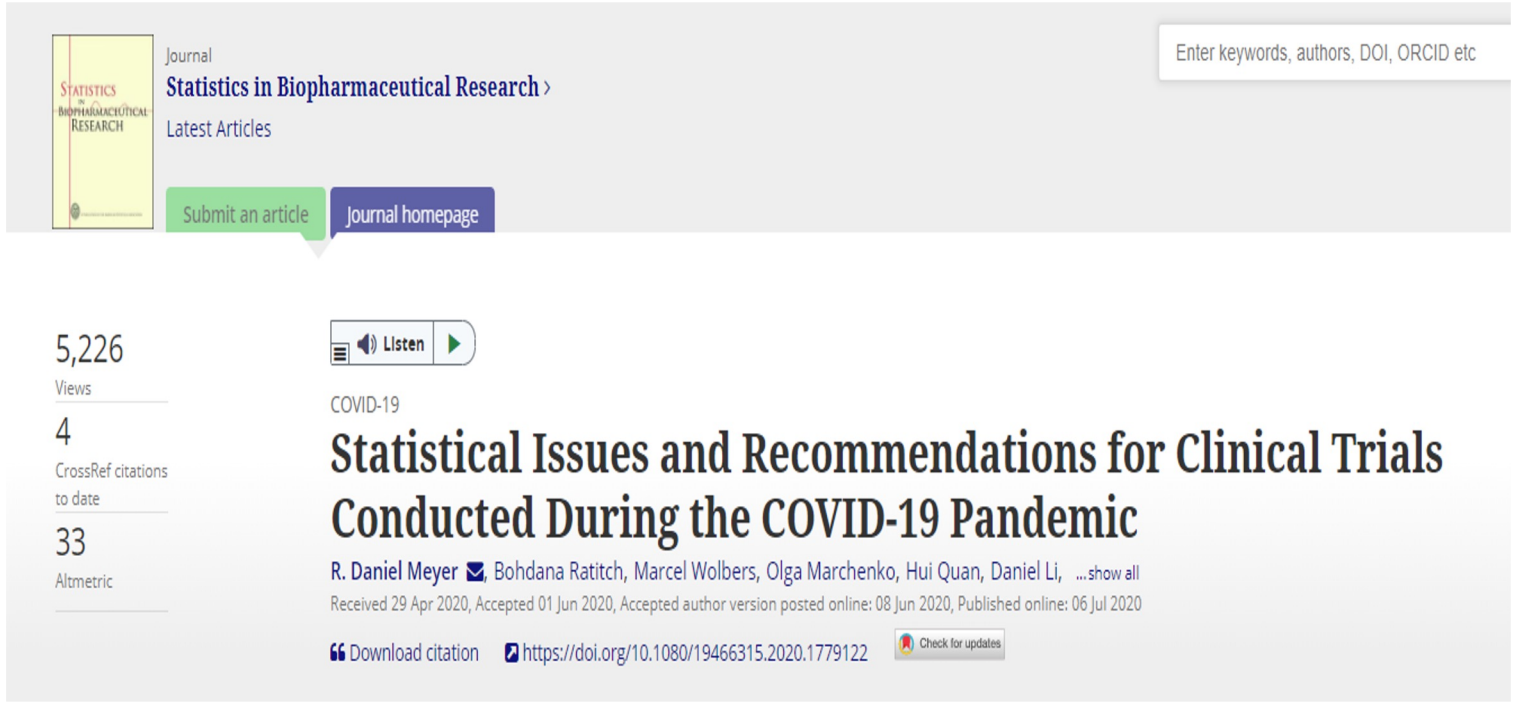
- 15 Companies
- 20 Statisticians
- 1 Goal







Pharmaceutical Industry COVID-19 Biostatistics Working Group



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Examples of Pandemic Impact

#	Factors	Risk/Impact
1	Quarantines, travel limitations, shelter-in-place, participant unable/unwilling to travel to site due to personal and/or pandemic-related reasons, site closures or reduced availability of site staff	• Missed or delayed visits and assessments/Loss to follow-up • Inability to access study treatment • Longer query response time/Delayed site monitoring • Different investigators / different measurement modalities
2	Interruptions to supply chain of experimental drug and/or other medications	• Missed dosing of study drugs • Changes in non-COVID-19 concomitant medications
3	Alternative administration of drug	• Increased risk of dosing errors • Lack of equivalence of methods of administration
4	Alternative collection of specimens	• Challenges in reconciliation and verification
5	Alternative data collection	• Lack of exchangeability of methods
6	COVID-19 infection / treatment	• Temporary / permanent interruption of study treatment and/or study participation • Potential effect on efficacy endpoints /estimands / safety • Interactions of COVID-19 concomitant medications with study drugs

Note: See Table 1 of the SBR manuscript

Roche/Genentech Internal Efforts

Two sources of pandemic-related impact

1. **Systematic disruptions of health care systems (“indirect” impact)**
    - Issues related to study treatment adherence and accessibility due to participant, physician, or site decisions, or drug supply issues
    - Logistic issues at site or participant’s fear causing missing visits or visits using alternative means of assessment
2. **Participants COVID-19 infection condition and treatment (“direct” impact)**

In many settings, **source 1** will have the **predominant impact** on trials. **Impact** expected to be **largest** in trials in **not life-threatening diseases in older and frail participants** (but both sources need to be considered in all trials).

Source: Roche internal guidance - Analysis Considerations for studies impacted by COVID-19”.

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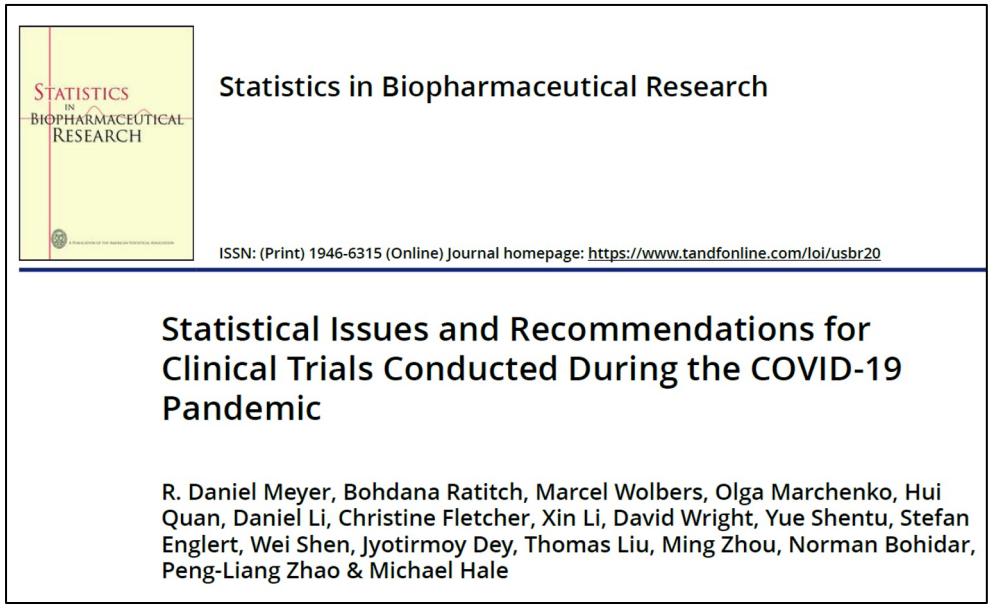
Efficacy Analyses:
Using Estimand Framework to Handle Impact of COVID-19

Marcel Wolbers, Ph.D., Expert Statistical Scientist, Roche/Genentech
Chin-Yu Lin, Ph.D., Director of Biostatistics, Roche/Genentech

Acknowledgements



...but views and opinions expressed in the following slides are those of the presenter.

Prerequisite: Aggregated risk assessment

- First priority: Accurate **data collection documenting pandemic disruptions** (focusing on **critical variables** affecting trial integrity)
- **Blinded summaries** of impacted critical variables
  - Study treatment interruptions and discontinuations, study withdrawals
  - Missed, delayed or deviant (i.e. via alternative modalities) assessments
  - COVID-19 infections, deaths, concomitant medications
- Assess impact on
  - Study **interpretability**
  - Planned **estimands** and **analyses**
  - Study **power** and probability of success
  - Study **timelines**

Possible mitigations measures

- **Mitigation measures** may include
  - Changes to planned estimands or analyses
  - Temporary halt of recruitment
  - Increases in sample size or follow-up, or replacement of non-evaluable participants to compensate for power loss
  - Changes in read-out timelines
- Implemented mitigations need to be **documented** in protocol and/or SAP
- Pro-active **engagement of health authorities** recommended if substantial changes are planned

- **Focus of this presentation**: Changes to planned efficacy **estimands** and **analyses**

Does the pandemic change my trial objective?

- Clinical trial findings should inform regulatory/HTA decisions based on the applicability to future clinical settings **without the acute, systematic disruptions to the healthcare systems** in a global disaster.

- This leads to a **reaffirmation of the original research question**:
  - How would Drug A compare to Drug B **in the absence of COVID-19 pandemic**?
  - In specific situations: How does Drug A compare to Drug B **in the presence of possible individual COVID-19 infections**?

Can I ignore pandemic disruptions in my analysis?

- Ignoring pandemic-related impacts in data collection and analysis may result in estimating a **treatment effect confounded by pandemic-related factors**.
  - Inference may not align with the original scientific question
  - Study conclusions may not be generalizable to post-pandemic clinical care

- Challenge: How do we **account for the pandemic-related disruptions** yet **remain consistent with the study objectives**?

Example

- Imagine a Ph 3 study of an experimental treatment as an add-on to a standard background therapy in patients with moderate/severe Chronic Obstructive Pulmonary Disease (COPD)
- Long-term symptom control (over one year) needs to be demonstrated

Plan before the pandemic

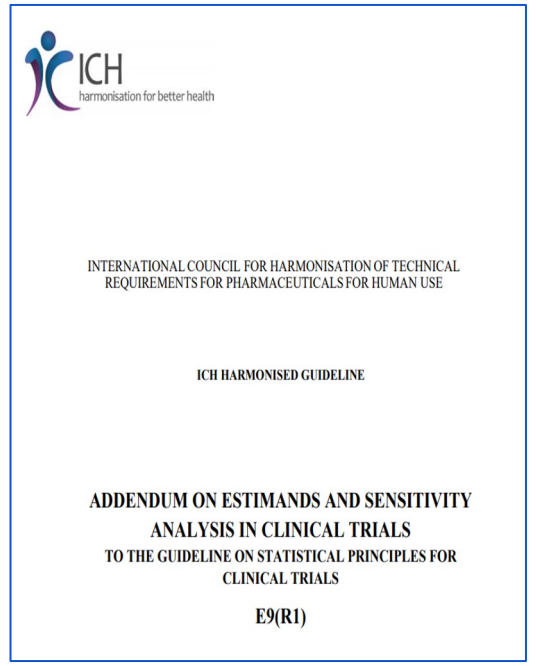
- It was anticipated that most study treatment discontinuations would be due to treatment-related reasons (lack of efficacy or toxicity).
- There are no effective treatment alternatives for participants who discontinue randomized treatment prematurely - expected to remain on the background therapy only.
- Effect of incomplete treatment on the endpoint measured over one year is of interest.
- Thus, all treatment discontinuations were planned to be addressed using the **treatment policy strategy**, i.e. the observed one-year outcomes are used in the analyses regardless whether the subject discontinued study treatment or not.

Reality during the pandemic

- In the context of COVID-19 pandemic, participants may also discontinue study treatment due to:
  - Site operation disruptions
  - Participant's perception of increased risk versus benefit from the study participation
  - Complications of COVID-19 infection and start of COVID-19 therapy in a hospital setting
  - COVID-19 death
- **Should all the above discontinuations also be addressed by the treatment policy strategy?**

ICH E9 (R1) estimand framework

- A **structured means** to describe the **study objective** and to **define the targeted treatment effect** using **five attributes**
- A **systematic framework** to **assess pandemic impacts**, to **ensure that mitigation strategies align with the study objectives** and as b**asis for regulatory discussions**
- The estimands framework may also be relevant for studies where estimands were not formally defined


ICH
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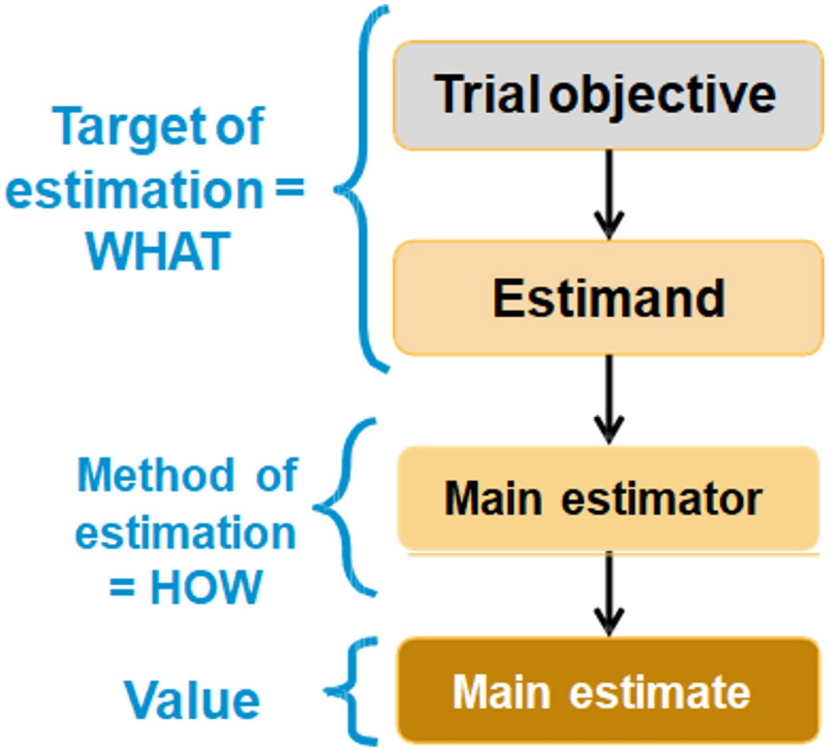
INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS
TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9(R1)

Estimand framework



5 estimand attributes

Population

Subjects targeted by the scientific question

Variable (or endpoint)

Measure(s) required to address the scientific question (to be obtained for each subject)

Treatment

The treatment of interest, and if appropriate, the alternative treatment to which comparison will be made

Remaining Intercurrent events

The specification of how to account for other intercurrent events reflecting the scientific question of interest

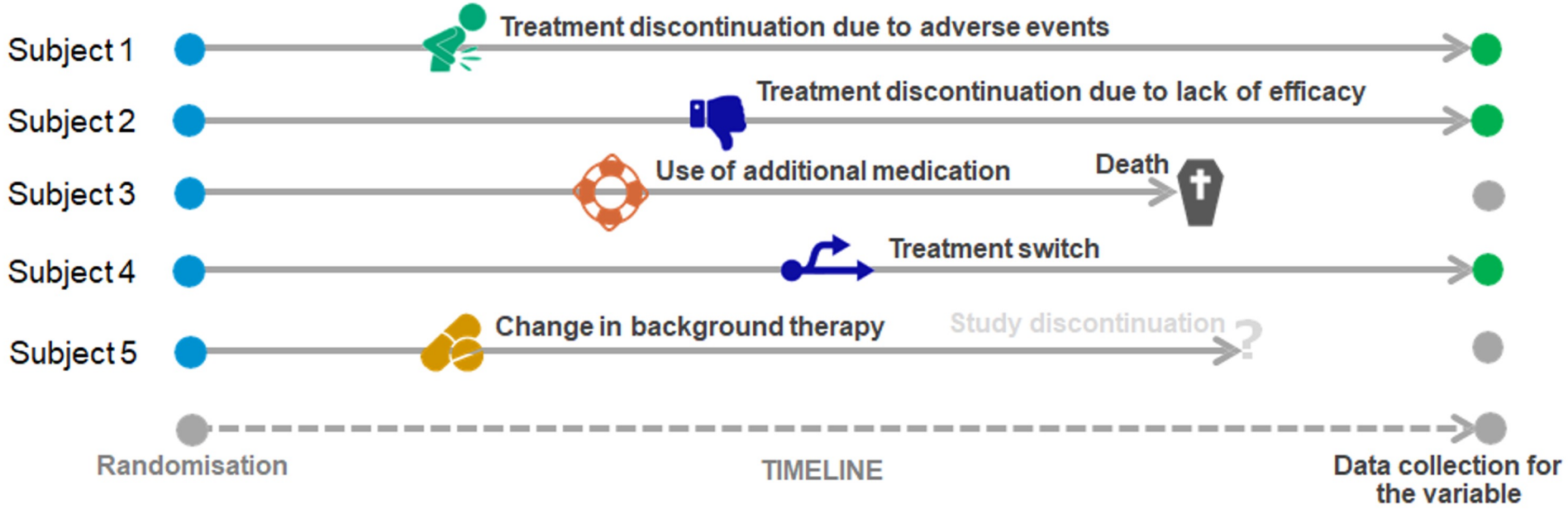
Population-level summary for the variable

Provides, as required, a basis for a comparison between treatment conditions

ICH E9.R1 training material

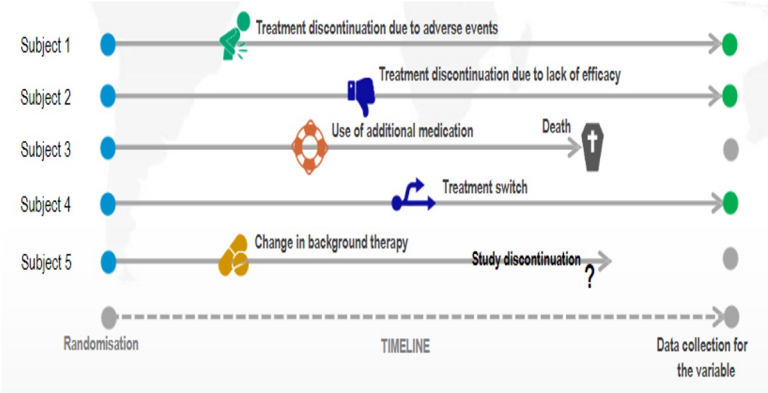
Most likely affected estimands attribute: Intercurrent events (ICEs)

- "Events **occurring after randomization or treatment initiation** that **affect** either the **interpretation** or the **existence** of the measurements associated with the clinical question of interest."
- Examples (from ICH E9.R1 training material):



Examples of pandemic-related ICEs

- Pandemic-related study treatment **discontinuations**
  - due to systematic pandemic disruptions of health care systems
  - due to subject's s COVID-19 infection condition
- Pandemic-related study treatment **interruptions**
- COVID-19 **infection** and **concomitant medications**
- COVID-19 associated **deaths**



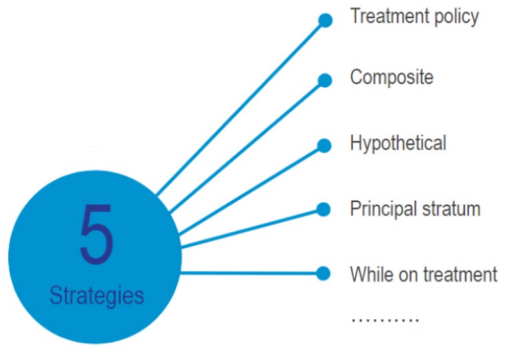
5 strategies for addressing intercurrent events (according to ICH E9.R1)

- **Composite strategies**, impacting the variable definition
- **Principal stratum strategies**, impacting the population definition

- **Treatment policy strategies**, disregarding ICEs
- **Hypothetical strategies**, assuming ICE hadn't happened
- **While on treatment strategies**, considering until ICE

Strategies to handle non-pandemic versus pandemic ICEs

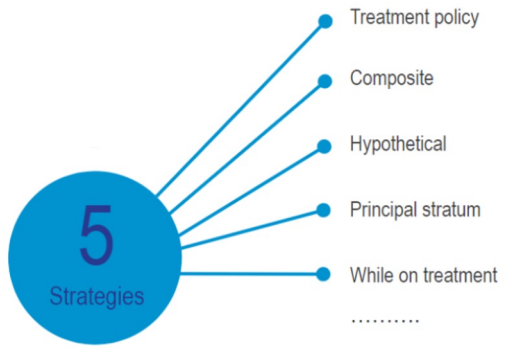
- Non-pandemic related ICEs: Recommended to use the strategy planned in the original study protocol
- Pandemic-related ICEs: Even if a strategy for a corresponding non-pandemic related ICE (e.g. treatment discontinuation or deaths) has been pre-defined, the same strategy may not be applicable if the ICE is pandemic-related
- A **hypothetical strategy** ("as if the ICE had not happened") is a natural choice for many pandemic-related ICEs



Tentative suggestions for handling specific pandemic ICEs

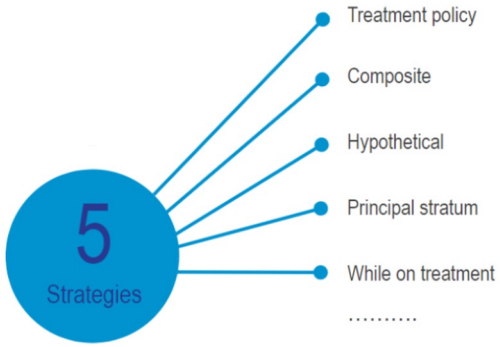
- Pandemic-related **study treatment discontinuations**
  - If frequency is negligible: use same strategy as for non-pandemic discontinuations
  - Otherwise: Hypothetical strategy (this may differ from handling of non-pandemic-related discontinuations!)

- Pandemic-related **study treatment interruptions**
  - Strategy depends on disease area and PK/PD of study drug
  - One possibility
    - Define minimal interruption duration expected to dilute the treatment effect
    - If interruption shorter than threshold: treatment policy strategy (“disregard”)
    - If interruption longer than threshold: hypothetical strategy



Tentative suggestions for handling specific pandemic ICEs (continued)

- **COVID-19 related deaths**
  - Diseases with minimal mortality: hypothetical strategy may be recommended
  - Severe disease where death is part of the endpoint: hypothetical strategy is most appropriate for estimating the treatment effect in the absence of the pandemic. However, COVID-19 related deaths may be rare in many settings and COVID-19 relatedness may be difficult to adjudicate. Hence a composite strategy (i.e. treating COVID-19 related deaths in the same way as other deaths) may be a pragmatic alternative.



- Appropriateness of the above suggestions needs to be **reassessed on study-level**

Missing and unobservable data

- Despite best efforts, sponsors should prepare for the possibility of **increased amounts** and/or **distinct patterns** of **missing data** due to
  - missed assessment
  - incomplete assessments
  - delayed, out-of-window assessment
  - withdrawal from study
- Missingness is not an ICE in itself
- Missingness may or may not occur with an ICE
- Target outcomes after the ICE are **unobservable** under hypothetical scenarios

  [methods for modeling unobservable outcomes are usually the same as those for handling missing data]

Missing data mechanisms for pandemic-related missing data

- In most cases, a **MAR or MCAR assumption** is **plausible for pandemic-related missing data**
  - MCAR (missing completely at random): probability of missingness may depend on baseline characteristics but does not depend on either the observed or unobserved outcomes
  - MAR (missing at random): probability of missingness may depend on baseline characteristics and observed outcomes but not on unobserved outcomes
  - If MAR or MCAR holds, then missing values can be modelled based on available data from “similar” participants

- Many **statistical approaches** available
  - **Time-to-event, binary, count data** [for MCAR]: Cox, logistic, negative binomial models
  - **Longitudinal data** [for MAR]: Linear mixed effects models, MMRM
  - **General approach** [for MAR]: Multiple imputation (imputation model can adjust for auxiliary variables without including them in the analysis model)

An example when MAR may not be appropriate

Context:

- Participant in a COPD study discontinued study treatment due to an adverse event (AE) and was expected to be followed through the end of study (per treatment policy strategy for this ICE).
- Participant initially stayed in the study but some time after the start of the pandemic decided to withdraw from the study.
- Participant's reason for study withdrawal was that, in their view, their condition deteriorated and they are worried that visiting clinic for study procedures would increase their risks associated with COVID-19.

Strategy for handling missing values:

- As participant discontinued due to AE, the early efficacy outcomes may have been favorable, but would be expected to worsen after study treatment discontinuation. These worsened outcomes are not (fully) captured and may be more severe than in participants who remained in the study. Therefore, modeling under MAR may not be appropriate.
- A MNAR (Missing Not at Random) approach could assume worse outcomes than what would be predicted based on a model from participants who discontinued study treatment but remained in the study.
- The extent of "worse" should be clinically plausible and investigated in sensitivity analyses.

Some considerations for sensitivity analyses

- **For time-to-event endpoints:** Recommended to use **interval-censored methods** for endpoints that rely on regular assessments (e.g. PFS) as sensitivity estimators because they are less affected by missed or delayed assessments.

- Beware that **pre-defined sensitivity analyses may become excessively conservative** if the amount of pandemic-related missing data is large. Therefore, consider **separate handling of non-pandemic and pandemic-related missingness** (in line with the estimand), e.g.
  - Tipping point analyses may only tip non-pandemic missing data
  - Conservative treatment of missing data as non-responders for binary endpoints may only be used for non-pandemic missing data (and multiple imputation under MAR for pandemic missing data)

Example: Phase III Trials with a Continuous Endpoint

Original Plans

- Study design:
  - Multiple Phase III, randomized, active controlled trials
  - Patients are treated either at fixed intervals or on a flexible dosing regimen
  - Efficacy assessments are done every 4 weeks
  - The primary endpoint is a continuous variable at week 52
- Original Statistical Analysis Plans
  - **Treatment Policy Estimand** with the following intercurrent events (ICEs)
    - Use of prohibited medications
    - Treatment discontinuation due to lack of efficacy or due to AEs
  - Primary analysis using MMRM. Missing data will be implicitly imputed.

Example: Phase III Trials with a Continuous Endpoint

Impact of COVID-19

- Anticipated Impacts of COVID-19
  - Patients missed protocol scheduled visits and assessments
  - Patients missed study drug administration
  - Patients used standard of care treatment (prohibited therapy)
  - Patients discontinued treatment or discontinued study
  - Patients with confirmed or suspected COVID-19 infections and/or received COVID-19 related meds
  - Patients died of COVID-19

- Assessment of COVID-19 Impact *
  - # confirmed or suspected COVID-19 cases is low
  - % patients with > 1 missed dose is expected to be low
  - Missing data is estimated to be at most up to 20-30% at any visit through primary analysis timepoint

* depending on the pandemic development

Example: Phase III Trials with a Continuous Endpoint

Revised Plans

- For non-pandemic related ICEs, **treatment policy strategy** will be applied as planned
- Add pandemic related ICEs and apply **hypothetical strategy**:
  - Pandemic related ICEs include
    - Use of prohibited therapy due to COVID-19
    - Treatment discontinuation due to COVID-19
    - Missed dose(s) with potentially major impact on efficacy, due to COVID-19
    - COVID-19 related deaths
  - Primary analysis will still be using MMRM. Missing data will be implicitly imputed.

- Supportive analyses
  - Sensitive analysis, using different rules to handle missing/unobserved data
    - LOCF
    - Multiple imputation assuming MAR for COVID-19 related ICEs and non-MAR for the other ICEs
    - Trimmed mean method (truncating patients with the worst outcome, with the assumption that patients have the worst outcome after non-pandemic related ICEs (Permutt and Li 2017)
  - Supplemental analysis, using treatment policy estimand for all ICEs
    - Relatedness to COVID-19 may not be accurately assessed

Although hypothetical strategy is used for COVID-19 related ICEs, it's recommended that data collection continues after ICE as these data may be needed in supportive analyses

Summary

- **Accurate data collection** documenting pandemic disruptions and an **aggregated risk assessment** (usually based on blinded data) is the **basis for any mitigation steps** for pandemic disruptions including modifications in planned efficacy analyses
- The **estimand framework** provides a **systematic pathway for addressing the impact of the pandemic**
- The definition of a **hypothetical strategy** for pandemic-related ICEs is a natural way to investigate the effect of a treatment in the absence of the pandemic
- Most pandemic-related missing/unobserved data is likely **MCAR** or **MAR**
- The appropriateness of all planned analyses (including **sensitivity analyses**) should be **re-examined** in view of the pandemic

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  - **Chin-Yu Lin, Ph.D., Director of Biostatistics, Roche/Genentech**
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Tools to Assess Impact of COVID-19 on Data Integrity and Interpretability

Zoe Zhang, Ph.D., Principal Statistical Scientist, Roche/Genentech
Chin-Yu Lin, Ph.D., Director of Biostatistics, Roche/Genentech

Outline

- Considerations for Assessing the Potential Impact of COVID-19 on Ongoing Trials
- Examples
  - Quick Reaction: Preparation of Primary Analysis for a Phase III Trial
  - Ongoing Efforts: Monitor Impact of COVID-19 for Ongoing Phase III Trials
- Summary

Outline

- **Considerations for Assessing the Potential Impact of COVID-19 on Ongoing Trials**
- Examples
  - Quick Reaction: Preparation of Primary Analysis for a Phase III Trial
  - Ongoing Efforts: Monitor Impact of COVID-19 for Ongoing Phase III Trials
- Summary

Considerations for Assessing the Potential Impact of COVID-19

- **Ongoing clinical trials are impacted differently**
  - disease area / patient population
  - treatment regimen
  - lifecycle of the study
  - endpoint(s)
- **Direct** impact from the COVID-19 infections
  - Trial participants who had or suspected to have COVID-19 infections, death, and concomitant medications
- **Indirect** impact from the COVID-19 pandemic
  - Trial participants movement restricted
  - IMP shipping delayed/blocked
  - Sponsor/site actions

Direct Impact

- **Data reporting / collection**
  - Work closely with the sites to ensure sufficient information on (potential) COVID-19 infections are collected for safety reporting
  - Utilize existing case report form for Adverse Events to collect confirmed or suspected COVID-19 infections
  - MedDRA dictionary v23.0 and afterwards updated to include COVID-19 related coded terms
- **Data analyses**
  - Subjects with confirmed or suspected COVID-19
  - COVID-19 associated AEs via windowing

Indirect Impact (1)

New

- **Data reporting / collection**
  - Systematic capture of protocol deviation is essential to enable the assessment of the indirect impact
  - Major protocol deviations that could potential affects the study integrity are defined prior to the pandemic (updates to the data collection may be needed to categorize pandemic related deviations)
  - Minor protocol deviation may need to be reviewed to assess the impact

Indirect Impact (2)

- **Data analyses to assess the impact on study treatment exposure/endpoints assessment**
  - Protocol deviation collection links the missed visits/assessment with COVID-19 pandemic related reasons
  - Consider splitting the analyses into pre-pandemic, during pandemic and post-pandemic timeframes
  - Consider characterizing how the exposure/endpoint assessments would have been in the absence of the COVID-19 pandemic
  - Deep dive into the data to assess the impact might be needed

Example: Impact on Tumor Assessments

Time Period
Before 01DEC2019
Number of TA expected
Number of TA Completed
01DEC2019 to CCOD
Number of TA expected
Number of TA Completed

Thus far, oncology clinical studies have not seen major impact from the pandemic

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Number of censored patients who have not discontinued study treatment with time between the last adequate tumor assessment date and the clinical cut-off date >= 90 days
Total
Number of patients censored before 01 December 2019
Number of patients censored on/after 01 December 2019
Number of patients with an event occurring after two or more missing tumor assessment
Total
Number of patients with an event reported before 01 December 2019
Number of patients with an event reported on/after 01 December 2019

Outline

- Considerations for Assessing the Potential Impact of COVID-19 on Ongoing Trials
- **Examples**
  - **Quick Reaction: Preparation of Primary Analysis for a Phase III Trial**
  - **Ongoing Efforts: Monitor Impact of COVID-19 for Ongoing Phase III Trials**
- Summary

Two Examples

Example 1: Quick Reaction

- Primary analysis expected in Q2, 2020
- A desire to maintain the timeline
- Not prep for the COVID-19 pandemic impact
- Urgent need for a tool

Example 2: Ongoing Efforts

- Primary analysis expected later of the year
- More time to develop efficient tools to monitoring the trial
- More time to understand the pandemic impact

Example 1

- Questions to be addressed prior to the primary analysis
  - What's the impact of COVID-19?
  - How to ensure the data quality (data completeness and cleanliness) are up to standards for filing?
  - Did the analysis plan need to be modified to account for the impact of COVID-19?
  - What's the site status? How many sites were closed? For sites that were opened, did they have staffs to support patient visits, data entry and data cleaning?
  - Did we need to postpone the primary analysis?

Example 1: Critical Factors

- The following factors were considered critical to assess the impact of COVID-19.
  - Missing data
  - Treatment disruption/discontinuation
  - Major and minor COVID-19 related protocol deviations
- An Excel site tracker was created to
  - Track the status (open vs. close) for each site
  - Track upcoming primary endpoint visit dates and whether visits occurred

Example 1: Critical Factors

Track # Patients with Missed Visits

Visit	# Patients Expected	# Patients with Data	# Patients missed the visit	# Patients with No data entry
Random	500	500	0	0
Week 4	500	500	0	0
Week 8	499	496	1	2
Week 12	498	493	2	3
Week 16	495	490	1	4
Week 20	490	485	1	4
Week 24	490	480	5	5
Week 28	488	460	10	18
Week 32	488	453	15	20
Week 36	482	450	12	20
Week 40	480	440	10	30
Week 44	480	430	?	
Week 48	480	400	?	

Example 1: Critical Factors

Track # Patients with Missed Assessments by Assessment Type

CRF:	Primary Endpoint Assessment			Key Secondary Endpoint Assessment			…
Visit	# Patients with Data	# Missed Form	# Forms Pending Data Entry	# Patients with Data	# Missed Form	# Forms Pending Data Entry	…
Randomization	500	0	0	500	0	0	
Week 4	500	0	0	500	0	0	
Week 8	496	1	2	496	1	2	
Week 12	493	2	3	493	2	3	
Week 16	490	1	4	490	1	4	
Week 20	485	1	4	485	1	4	
Week 24	480	5	5	480	5	5	
Week 28	460	10	18	460	10	18	
Week 32	453	15	20	453	15	20	
Week 36	450	12	20	450	12	20	
Week 40	440	10	30	440	10	30	
Week 44	430	?		430	?		
Week 48	400	?		400	?		

Example 1: Critical Factors

Track # of Missed Doses and Early Treatment Discontinuation

CRF:	Study Drug Administration			Study Drug Completion/Early Discontinuation		
Visit	# Patients with Data	# Missed Form	# Forms Pending Data Entry	# Patients with Data	# Missed Form	# Forms Pending Data Entry
Randomization	500	0	0	0	0	0
Week 4	500	0	0	1	0	0
Week 8	496	1	2	0	1	0
Week 12	493	2	3	1	1	1
Week 16	490	1	4	2	1	2
Week 20	485	1	4	0	0	0
Week 24	480	5	5	0	1	1
Week 28	460	10	18	0	0	0
Week 32	453	15	20	1	3	2
Week 36	450	12	20	0	1	1
Week 40	440	10	30	0	?	
Week 44	430	?		0	?	
Week 48	400	?		0	?	

Example 1: Critical Factors

Track # Patients with Major COVID-19 Deviations

Major Protocol Deviations

Considerations:

- **Add COVID-19 related deviation subcategories**

Count of Protocol Deviations containing "COVID" in the descripton

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Study	Deviation Status	Category	Subcategory Name	All Issues	COVID-19 Related	Grand total
			SAE/AESI not reported to Sponsor within 24hr of discovery of ...	1	-	1

List of Major Protocol Deviations due to COVID-19

PDMS Details

Study	Country	Subject ID	Category	Subcategory Name	Decision	Trimmed Description (Current)

Example 1: Critical Factors

Review Patients with Minor COVID-19 Deviations and Upgrade Deviations to Major if Appropriate

Minor COVID-19 Related Protocol Deviations by Form

Count of CTMS Issues containing "COVID" in the descripton

Study	Deviation Type	Issue Level	Issue Type	All Issues	COVID-19 Related	Grand total
		Subject Visit	Informed Consent	-	1	1
			Non-Compliance	-	1	1
			Other	1	14	15
			PK Sample Collection & Storage	-	6	6

List of Minor Protocol Deviations due to COVID-19

CTMS Details

Study	Site Number	Subject ID	Visit Name	Deviation Type	Issue Level	Issue Type	Description

Add “COVID-19” in the beginning of deviation description

Example 1: Critical Factors

- The following factors were considered critical to assess the impact of COVID-19.
  - Missing data
  - Treatment disruption/discontinuation
  - Major and minor COVID-19 related protocol deviations
- An Excel site tracker was created to
  - Track the status (open vs. close) for each site
  - Track upcoming primary endpoint visit dates and whether visits occurred

Example 1: Data Quality

- Data completeness
  - Visits occurred but data were not entered (Track by form and visit)
- Data cleanliness
  - Due to limitation on site staffing, we defined critical variables and focused cleaning on these critical data up to the primary endpoint visits
- Use the site tracker to determine
  - Whether incomplete data entry and outstanding queries could be resolved prior to data snapshot

Example 1: Data Quality

Track # eCRFs Pending Data Entry

CRF:	Study Drug Administration			Study Drug Completion/Early Discontinuation			…
Visit	# Patients with Data	# Missed Form	# Forms Pending Data Entry	# Patients with Data	# Missed Form	# Forms Pending Data Entry	…
Randomization	500	0	0	0	0	0	
Week 4	500	0	0	1	0	0	
Week 8	496	1	2	0	1	0	
Week 12	493	2	3	1	1	1	
Week 16	490	1	4	2	1	2	
Week 20	485	1	4	0	0	0	
Week 24	480	5	5	0	1	1	
Week 28	460	10	18	0	0	0	
Week 32	453	15	20	1	3	2	
Week 36	450	12	20	0	1	1	
Week 40	440	10	30	0	?		
Week 44	430	?		0	?		
Week 48	400	?		0	?		

Example 1: Data Quality

Track # Outstanding queries by eCRF Form Type

Count of Queries by Form

Study	eCRF Form Name	Priority			Standard		
		# Queries Issued	# Queries Open	% Open Queries	# Queries Issued	# Queries Open	% Open Queries
	Targeted Medical History and Baseline Condi...	-	-	-	724	0	0.00 %
	Tobacco Use History	-	-	-	414	0	0.00 %
	Visit Date	77	0	0.00 %	3416	10	0.29 %

...

Example 1: Data Quality

Track the Status of Source Data Verification (SDV)

SDV by Form and Week

Study	Form	Randomization		Screening		
		# of CDF confirmed to have SDV	% Confirmed SDV	# of CDF expected to have SDV	# of CDF confirmed to have SDV	% Confirmed SDV
	Study Drug Completion/Early Discontinuation	-	-	-	-	-
	Subject Disposition	-	-	-	-	-

SDV by Form and All Visits

Study	Form	# of CDF expected to have SDV	# of CDF confirmed to have SDV	% Confirmed SDV
	Study Drug Completion/Early Discontinuation	40	12	30.0 %
	Subject Disposition	114	67	58.8 %

Two Examples

Example 1: Quick Reaction

- Primary analysis expected in Q2, 2020
- A desire to maintain the timeline
- Not prep for the COVID-19 pandemic impact
- An urgent need for a tool

Example 2: Ongoing Efforts

- Primary analysis expected later of the year
- More time to develop efficient tools to monitoring the trial
- More time to understand the pandemic impact

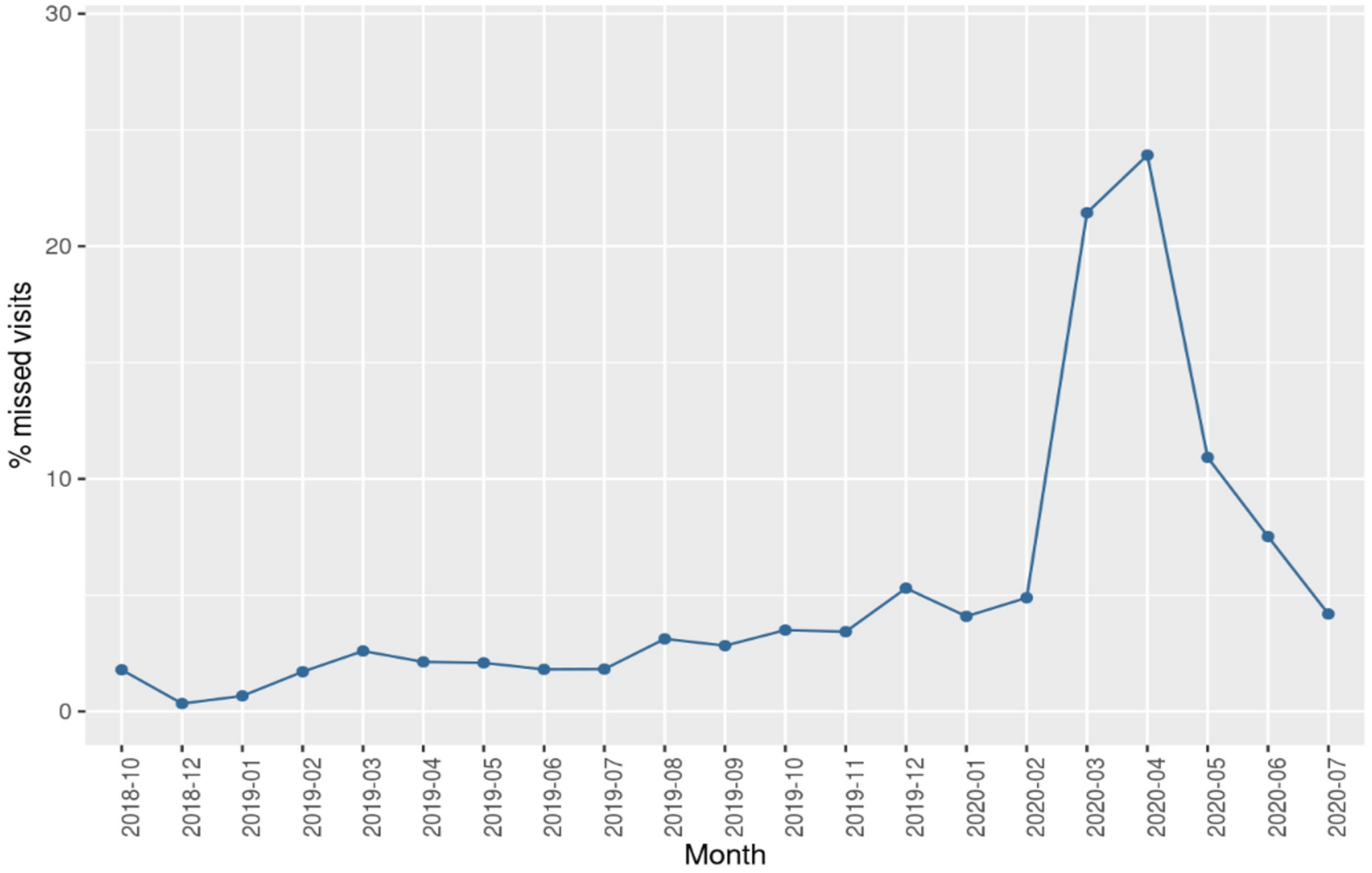
Example 2:

- Multiple Phase III trials are ongoing with an expected readouts at the end of the year
- Higher % of missed visits due to imposed COVID-19 restrictions

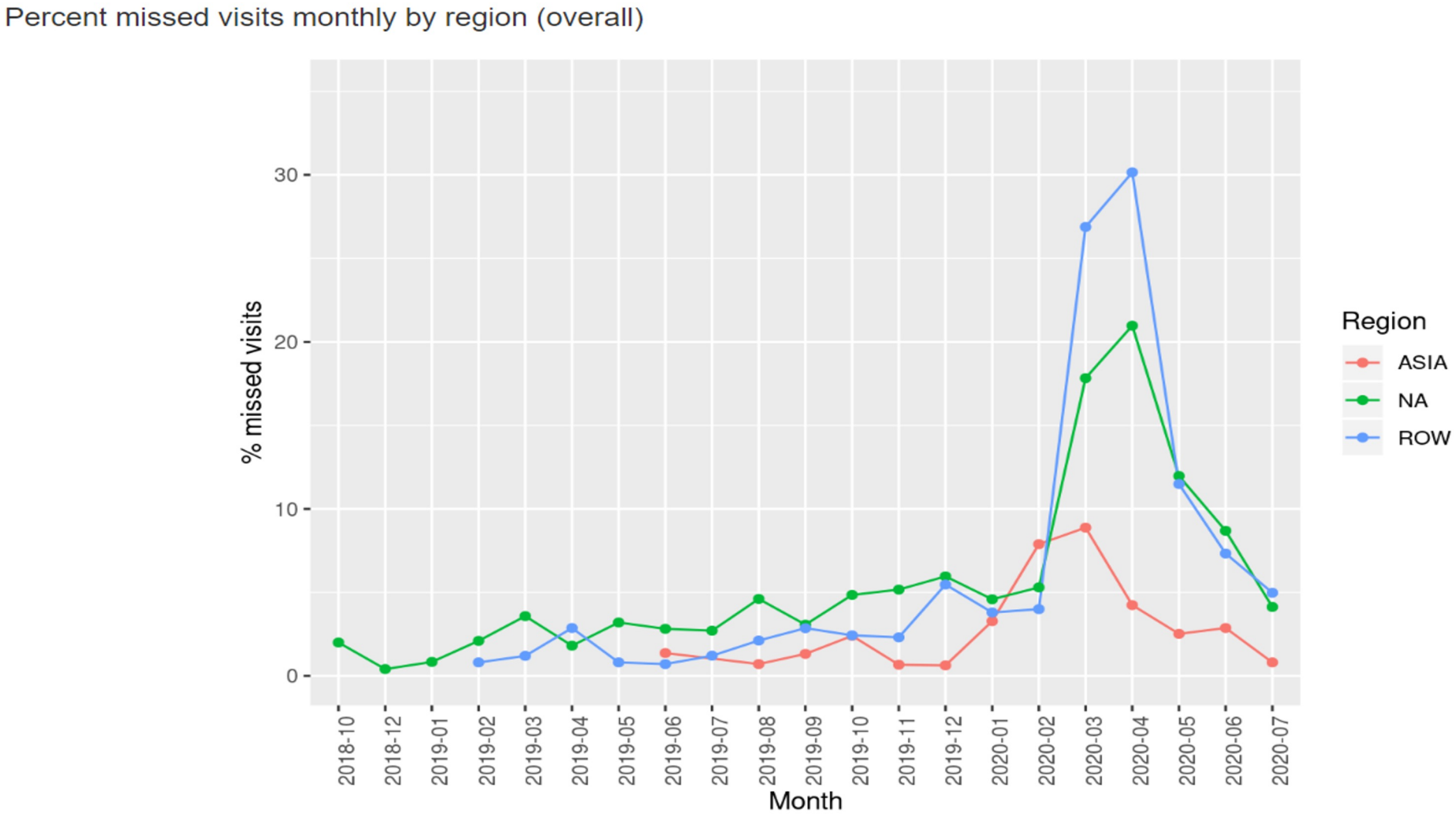
- R programs were created to track and assess the impact of COVID-19 based on
  - Missed visits
  - Missed doses
  - Early treatment discontinuations

- A Spotfire tool was created to assist the review and identification of COVID-19 related protocol deviations

Example 2:
R Outputs: Track % Missed Visits by Calendar Time

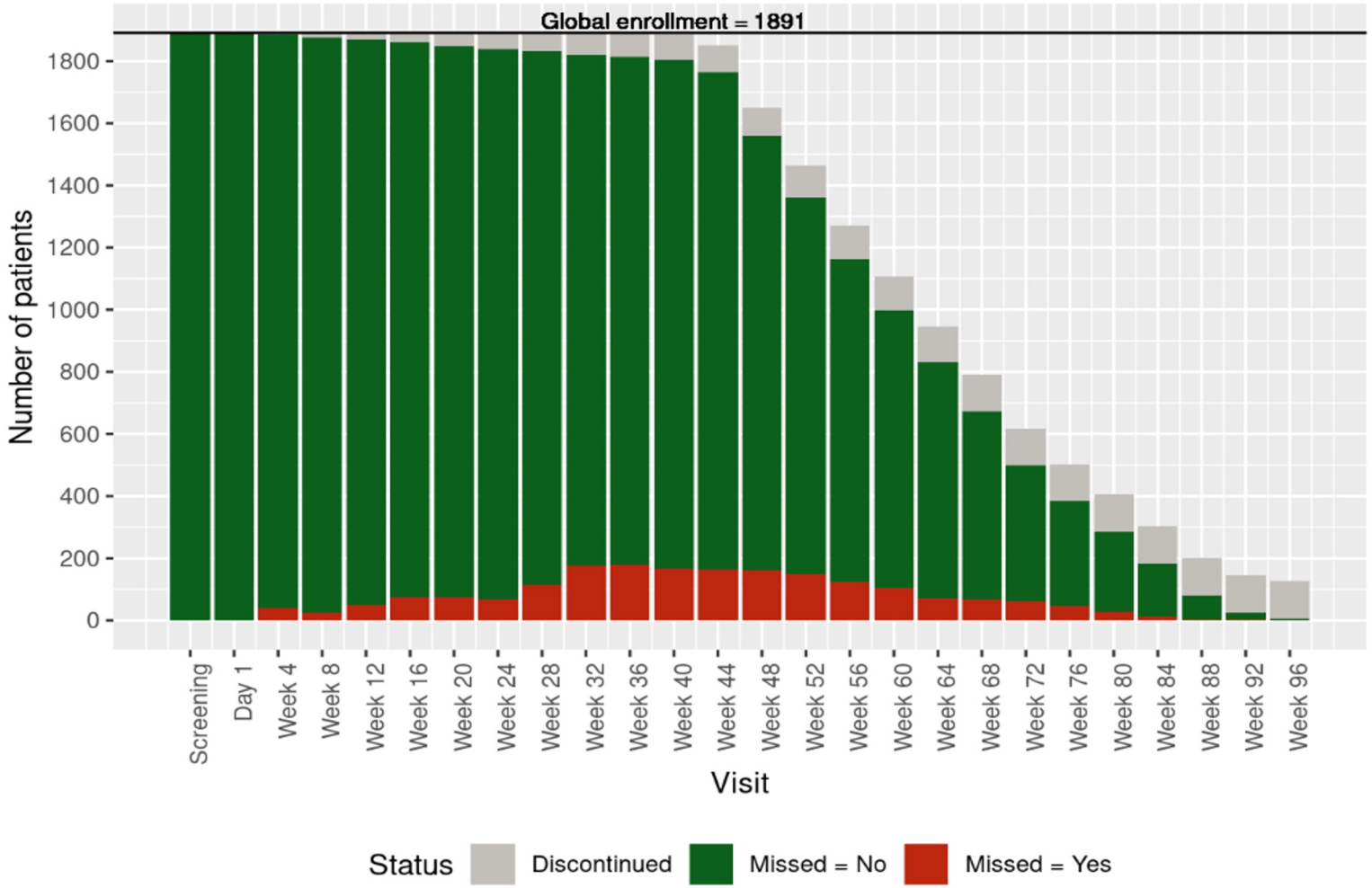


Example 2:
R Outputs: Track % Missed Visits by Region and Calendar Time



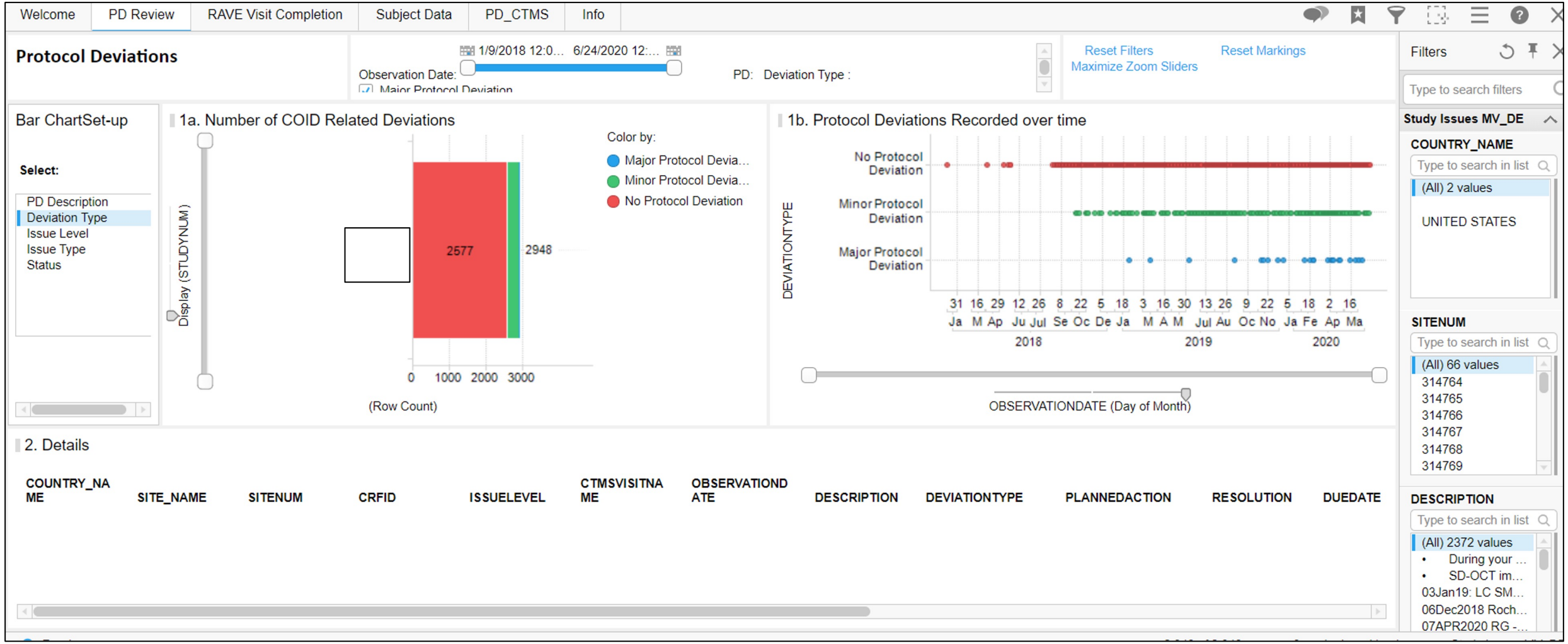
Example 2:
R Outputs: Track # Patients with Missed Visits and Early Treatment Discontinuation

Barplot of Number of patients by Visit and Visit status



Example 2:

Spotfire: Tool to Assist Review and Identification of COVID-19 Related Protocol Deviations



Summary

- COVID-19 affects studies to different degrees
  - Immediate actions are needed to ensure patient safety and maintain trial integrity
  - Enhanced data capture methods needed to understand the impact of the pandemic
  - Require ongoing evaluation of the extent of the impact
- COVID-19 may also impact data quality (data completeness and cleanliness) due to limited site resources
- Tools can be helpful to monitor the impact of COVID-19 and data quality
- Lessons Learned
  - Encourage timely data entry
  - Ongoing intensive data cleaning

Outline

- Introduction
- Efficacy Analyses: Using Estimand Framework to Handle the Impact of COVID-19
  - Marcel Wolbers, Ph.D., Expert Statistical Scientist, Roche/Genentech
  - Chin-Yu Lin, Ph.D., Director of Biostatistics, Roche/Genentech
- Tools to Assess Impact of COVID-19 on Data Integrity and Interpretability
  - Zoe Zhang, Ph.D., Principal Statistical Scientist, Roche/Genentech
  - Chin-Yu Lin, Ph.D., Director of Biostatistics, Roche/Genentech
- **Summary**

Summary

ASSESS	• Diligently assess every COVID-19 pandemic impact on the clinical trial design, conduct, analysis and interpretation. • Tools can be useful to understand the impact • For efficacy analysis, the estimand framework provides a systematic approach to assess the pandemic impact.
ACT	• Fully understand the risks and have a fit-for-purpose mitigation plan and act correspondingly. • Pandemic-related ICEs will likely need to be defined to properly and rigorously account for the pandemic effect. • The appropriateness of all planned analyses (including sensitivity analyses) should be re-examined in view of the pandemic. • Supplementary analyses may be needed to fully understand the treatment effect.
CONSULT	• Engage early with Health Authorities on changes and keep the communication channel open.
DOCUMENT	• Clearly document the actions and the rationales.

Doing now what patients need next