COVID-19 pandemics : Impact on Clinical Trials in a chronic progressing disease

Paul Delmar, 16 June 2021

Disclaimer

- My own personal views
- Do not represent the views of Roche

Introduction

Study Design and Protocol Changes

Study Conduct and Monitoring

Study Reporting and Analysis

Introduction

- 1.5 year into the COVID-19 pandemic
- Potential impact on clinical trials was recognized very early on
- It has generated an abundance of publications, presentations, comments,...
- PSI Neuroscience-Estimands European SIG : The impact of COVID-19 on clinical trials in NS
- BBS seminar (3 nov 2020, Andrew Hartley) : The impact of COVID-19 on studies in Neuroscience
- Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic (Daniel Meyer et al.)
- Clinical Trials Impacted by the COVID-19 Pandemic: Adaptive Designs to the Rescue? (kunz et al.)
- NOT a comprehensive overview or systematic review
  - **A reflection on my personal experience working in highly impacted late stage program in chronic progressive disease, and recent feed-back from health authorities**

Impact of COVID-19 Pandemics on clinical trials

Sponsor and HA have reacted promptly to mitigate risks and maintain study integrity

- Study Design and Protocol Changes
  - A large panel of different changes to study protocols were implemented
- Conduct and Monitoring
  - Collect pandemic related information and monitor the impact
- Reporting and Analysis
  - Adapt data analysis plan → Estimand, missing data ...

Regulatory Framework

Contains Nonbinding Recommendations

Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency

Guidance for Industry, Investigators, and Institutional Review Boards

March 2020

Updated on January 27, 2021

For questions on clinical trial conduct during the COVID-19 pandemic, please email Clinicaltrialconduct-COVID19@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)
Office of Good Clinical Practice (OGCP)

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 4

04/02/2021

Key changes from v3 (27-04-2020): remote source data verification

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Anti-Aβ Protofibrils Antibody lecanemab* (BAN2401)

Phase III Study Clarity AD (Early AD)

- Utilizing home infusion and telemedicine to secure safety and lower the burden for enrolled patients amid COVID-19 pandemic
- Increase sample size by approximately 200 to potentially mitigate the impact of patients who temporarily missed doses due to difficulty accessing research sites due to COVID-19, as well as to secure high quality data based on the consultation with FDA. This change was implemented without any knowledge of clinical results

The study seeks to obtain high quality data, while mitigating the impact of COVID-19

Current Primary Outcome Measures ICMJE **(submitted: June 15, 2020)**	Change From Baseline to Week 116 in Global Outcome, as Measured by Clinical Dementia Rating-Sum of Boxes (CDR-SOB) [Time Frame: Baseline up to Week 116]
Original Primary Outcome Measures ICMJE **(submitted: February 19, 2018)**	Change From Baseline to Week 104 in Clinical Dementia Rating-Sum of Boxes (CDR-SOB) Score [Time Frame: Baseline up to Week 104]

Expansion of home nursing capabilities in the GRADUATE trials

Substantial increase in number of sites and participants eligible for home nursing during COVID-19 pandemic

	Total number of participants enrolled	Total number of sites set up for HN	Number of participants enrolled at sites set up for HN	Number of participants eligible for HN at Week 12 at sites set up for HN	Number of participants eligible for HN at Week 16 at sites set up for HN
Pre-COVID (Sep 2019 – Feb 2020)	1,655	66	399	--	316
Peak-COVID (Mar 2020 – Aug 2020)	1,966	116	799	787	--

- The GRADUATE trials expanded the scope of HN allowing for more HN visits to occur
  - HN visits were allowed at Week 12, earlier than originally scheduled at Week 16
  - capacity and geographic availability of home nursing was increased

HN, home nursing.

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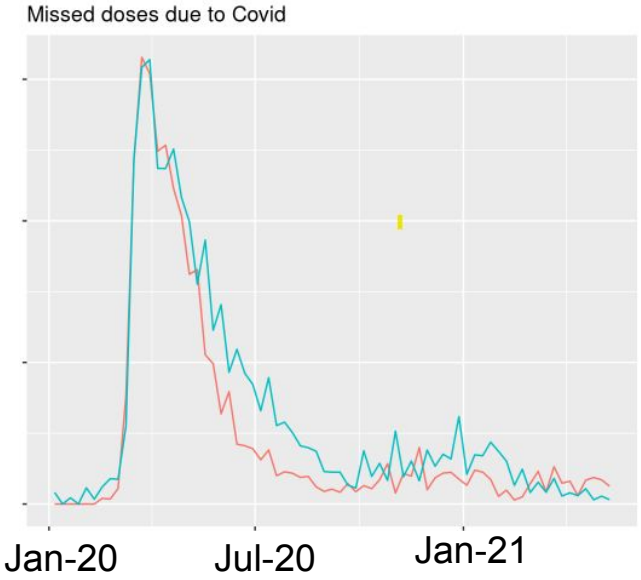
Monitoring Impact on Clinical Trial

Highest impact during the first wave Mar - Aug 2020



- Highest impact on missed dosing visits during the first wave
- Direct impact on study discontinuation relatively limited
- Collect and interpretation of pandemic related information is a big challenge
- The upgrade to the reporting systems and other learnings will have long term benefit after the pandemic

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- Pre-Specification
- Estimand and ICE
- Hypothetical Strategy

Challenges with Pre-Specification

First time reporting confirmatory study, with continuous primary endpoint, in the new estimand framework already a big challenge before the pandemic :

- Added complexity in dealing with ICE and missing data
- New terminology, new terms, documents templates not well adapted
- New data standards, etc….
- New statistical methods : Move away from well established, well accepted, tried and tested approaches (MMRM) to newer methodology, more complex, not as well understood, *sometimes relying on more assumptions*
- Some of these methods were used in sensitivity analysis before, some are completely novel. Use as the primary analysis increases the level of validation required
- The pandemic makes it even worse !

Challenges with Pre-Specification

- In principle, the confirmatory study is build on a wealth of accumulated information, which makes an informed and relevant full pre-specification possible
- How can we deal with the absolute uniqueness of the COVID-19 pandemic ? How can we fully pre-specify the analysis of a dataset strongly affected by COVID-19 pandemic in a way that is totally and absolutely unprecedented ?
- Is there an acceptable way to use blinded study data to inform the analysis (without “alpha spend”) ?
  - Regulators frown upon using blinded post-baseline data from the study for anything related to the primary analysis of the primary endpoint
  - Using only data on COVID related disposition and exposure but not on any post baseline efficacy ?

It does not seem possible, practical or desirable for the study statistician to be totally blinded to information about COVID impact on study conduct (missing dose, visit, drop out)

Challenges with Pre-Specification

"The applicant is advised to avoid dependence of the estimand definition on data from within the study." - EMA

"Given the uncertainties [...] in regard to the impact of the COVID-19 pandemic, our determination of the appropriateness of those approaches will in all likelihood be a matter of review" - FDA

"It is essential to investigate the impact of COVID-19 on the study using a range of estimands and sensitivity analyses. " - EMA

Estimand

- The pandemic has revealed the relevance and power of the estimand framework
- **“Treatment effect in a world without pandemics”** has been broadly advocated in the community
- This seems to be acceptable to HA for confirmatory pivotal trial, based on published guidelines and project specific feedback

“This is considered acceptable” - EMA

“The proposed primary estimand is acceptable in form” - FDA

Challenges in *categorizing* Pandemic Related ICE

Collecting the right information during study conduct is key, but very challenging

"The methods of identification of ICEs are also acceptable in principle, but there is some uncertainty whether the categorization will be sufficiently objective" - EMA

"We note that there could be a potential for the misclassification of COVID-19-related intercurrent events (ICEs)." - FDA

Challenges in *describing* Pandemic Related ICE

ICE	Challenge	Comment
Treatment withdrawal due to COVID-19 infection	Is this a safety/AE or a pandemic ICE ?	If treated as a pandemic event, does this open the door to refined classification of all safety related ICE ? Why COVID-19 but not any other unrelated AE ? On the other hand, this would obviously never have occurred in an “hypothetical world without pandemic”
Treatment interruption due to pandemic	ICE handling will depend on number of missed doses	a) Define ICE as “large number of missed doses” ? What to do with “small” number of missed doses ? - Trt Policy ICE (--> inconsistent with estimand) - Not an ICE ? Not defined as ICE ? b) Define one ICE of treatment interruption and put details in the estimator ?

Indirect impact of COVID-19 is difficult to capture in “traditional” ICE framework

- Emotional burden and change in participants environment could greatly impact PRO/CoA
- Many common CoA/PRO assess domains heavily affected by the pandemic situation (mental health, social interaction, activities of daily living,...)
- Mood disorder, sleep disorders, neurodevelopmental disorder and neurodegenerative, etc … could be particularly affected
- Other indirect effects of COVID could affect the validity of PRO :
  - Change in caregiver and rater
  - Change from in-person to remote data collection

Indirect impact of COVID-19 is difficult to capture in “traditional” ICE framework

“The difficulty of assessing the wider impact of COVID-19 on scale data is acknowledged [...]. Nonetheless, it needs to be justified that the technicalities are conservative, and dependency on assumptions is limited. “ - EMA

“we agree that the impact of COVID-19 on scale data may be appropriate to investigate further [...] lack of sufficient existing data [...]” - FDA

Hypothetical strategy for COVID related treatment interruption

1. Estimand
   a. Target of estimation: treatment effect in a world without pandemics
   b. → Hypothetical strategy

2. Estimator
   a. Treatment interruption → reduce treatment effect → loss of power ?
   b. “Standard” Hypothetical approach :
   c. Remove data after treatment interruption and impute using MAR

Hypothetical strategy for COVID related treatment interruption

"The Agency Guidance for Industry advises that [..] baseline information be used to exclude patients" - FDA

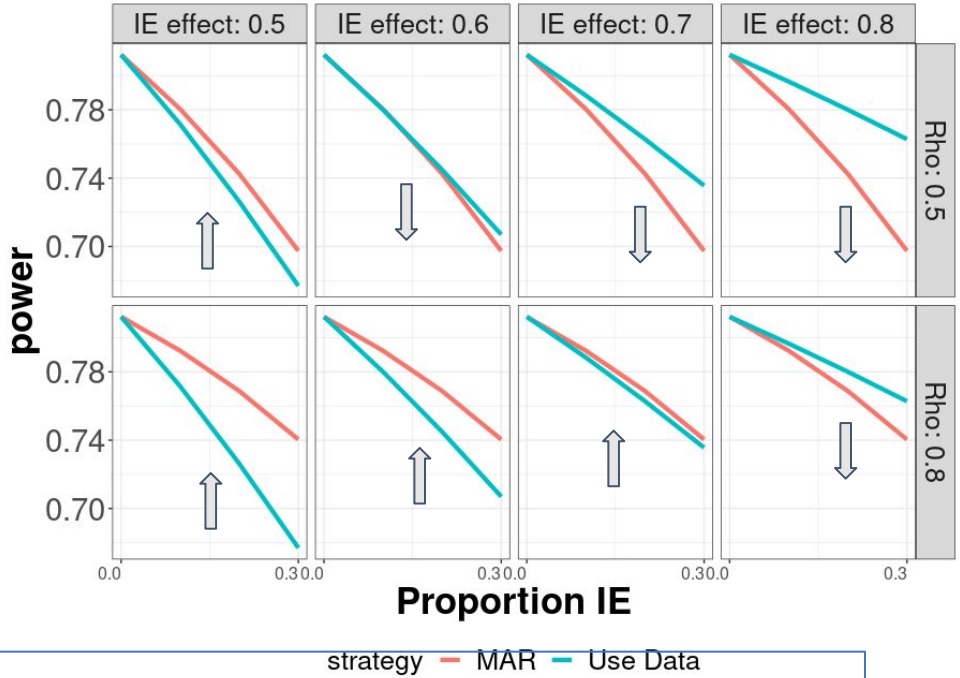
"It appears possible that the validity of the missing at random assumption could depend on calendar time " - FDA

"the hypothetical approach relies on assumptions [...]. These, if not true, may introduce bias to the estimation. Thus, the applicant is advised to *justify whether the approach is conservative*." - EMA

"This is a hybrid estimand [Trt Policy & Hypothetical], which *can be accepted given the relatively small amount* [...]. The applicant is made aware that a treatment policy estimand will be required [...] " - EMA

Power and hypothetical estimation

- **rho**: between visits correlation
- **IE Effect**: Proportion of "preserved" treatment effect after IE [0% -100%]



Whether or not MAR imputation improves power over using post-IE data depends on

1. **Proportion of preserved treatment effect after IE**
2. **The correlation between visits**

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Summary

- We start understanding the impact of the COVID-19 pandemic on clinical trial conduct: Missed visits, missed doses, missed assessments, etc...
  - Strong impact during the first wave, then more limited, scattered and differentiated
- **Indirect impact of the pandemic on PRO/CoA could be major**, depending on population on endpoint
  - Already some literature in a“real world” setting
  - **Clinical trial data not available yet**
- Estimand a great framework to think about and pre-specify the handling of COVID events but
  - also poses some challenges, w.r.t to consistent ICE definition and the dichotomy between Estimand and Estimator
  - **Industry and Regulatory Standards would be very valuable**

Summary

- The estimand era has prompted an increased sophistication in the handling of missing data, and complexity of analysis and pre-specification
- In case of a strong (direct and indirect) effect of pandemics, full pre-specification of the analysis is challenging because of the uniqueness of the situation
- Health Authorities is proactive and collaborative (guidance, meetings etc…)
  - But feedback can be a bit contradictory and confusing. Not pointing towards any potential solution
  - hypothetical strategy is accepted in principle but censoring data seems more problematic
  - Not willing to compromise on principles of pre-specifications
  - Use of (blinded) post randomization efficacy data to inform analysis is pretty strongly discouraged
- More discussion with HA are needed to understand the way forward for pivotal studies

Doing now what patients need next