Operational impact of COVID-19 on Clinical Trials

Natalie Dimier

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Overview

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Summary

General Thoughts

How are ongoing trials being impacted by COVID-19?

Direct COVID-19 Related Impact:

- COVID-19 infections and deaths within clinical trial participants, additional concomitant medication

Indirect COVID-19 Related Impact:

- Substantial increase in protocol deviations expected, both major and minor
- Increased use of telemedicine or alternative (local) hospitals
- Impacted supply of therapy and increased use of ‘prohibited’ medications
- Systematic disruption of healthcare systems
- Increased treatment/study discontinuation
- Lag in data entry and cleaning; increased use of remote monitoring
- High level of uncertainty as to when ‘normality’ will resume

Current Challenges

How to evaluate the (potential) impact of COVID-19?

- Systematic capture of protocol deviations is essential
  - Need to minimise site burden while evaluating impact on data integrity and interpretation
- With time lag for data entry, it is difficult to identify the extent of missing data
  - What is ‘currently’ missing versus ‘permanently’ missing?
- All clinical trials are impacted differently, depending on factors such as:
  - Disease area / patient population
  - Dosing regimen
  - Lifecycle of the study?
  - Endpoint(s)
- To some extent, lack of knowledge of the pandemic is also causing uncertainty in how to report

Potential Impact

What are we already observing?

- Substantial missed dosing will impact the ability of the study to test the underlying hypothesis
  - Generally difficult to mitigate or avoid
  - Study can quickly become non-interpretable
- Near-term focus on identifying how best to capture documentation around data missingness
  - How to handle such missing data in the analysis is longer-term goal
- Indirect impact of COVID-19 is difficult to measure
  - Impact of pandemic on mental health of patients
  - Impact and extent of COVID-19 imposed site restrictions
- Unclear what the long-term outlook for ongoing studies will be until the immediate restrictions of the pandemic are lifted

Example 1: Two Phase III confirmatory studies

- Two pivotal Phase III trials in a chronic disease in a high risk population
- Two years in duration with participants at all stages in the study
- Main impact: missed doses and efficacy assessments outside of window
- Working very quickly to assess if a protocol amendment is needed

Problems

- Access to sites and MRI centres is limited
- Frequent dosing: Q4W during up-titration and Q2W at target dose
- Tracking reasons for missed doses with existing systems is difficult
- Frequent MRI scanning is required particularly during up-titration phase
- Patients are still in screening

Solutions

- Home nursing: has always been available but we have increased availability
- Ability to use alternative MRI centres and local labs
- Continued dosing at the same level if MRI scan cannot be performed
- Screening extensions
- Possibility of Q4W dosing at target dose
- Increased flexibility in assessment time windows

Example 2: Phase III confirmatory study - non-inferiority

- Phase III non-inferiority trial in a frail population, sample size ~500
- Participants on ‘intervention’ arm initially treated like control arm but then receive an elective procedure
- To date, ~150 subjects randomized (90 intervention vs 60 control)
- COVID-19 impact
    - Trial intervention is prohibited at many sites during the pandemic →
      Subjects with elective procedure during pandemic continue to be treated as control
    - Recruitment and interventions put on hold but control arm operating as normal
    - At least 40-50 of the 90 currently enrolled intervention subjects will be non-evaluable for the primary non-inferiority comparison.

Mitigation Steps

Immediate and longer-term

- Identifying systematic yet pragmatic way to capture relevant information:
  - Documentation of missing data and relationship to COVID-19
  - Capture of COVID-19 infection cases, signs/symptoms or related AEs and disposition
  - Critical to minimise burden on sites and monitors
- Progressive enhancement of data capture ‘solutions’ as we start to gather data and evaluate how reliable and complete the information is
- Protocol amendments to ensure patient safety, but also consideration of statistical assumptions:
  - Sample size changes
  - Changes in the duration of follow up / time windows for dosing and assessments

Summary

- COVID-19 is affecting studies to different degrees
  - Immediate actions are needed to ensure patient safety and maintain dosing
  - Enhanced data capture methods needed to describe the impact of the pandemic
  - Require ongoing evaluation of the extent of the impact on missing data
  - Studies in chronic diseases and vulnerable patients are prone to be seriously affected
- We need to differentiate between immediate mitigation steps for studies/patients versus mitigation steps implemented only at the analysis stage
  - Made challenging when the long-term extent of the impact remains unclear
- Long-term impact on analysis strategies will be highly dependent on the steps taken now to capture the right information

Doing now what patients need next