Impacts of COVID-19 on Clinical Trial Monitoring – APRIL 2020

Current Snapshots from ACRO Member Companies

The data provided below was shared by individual ACRO's member companies. The data points rely on manual updates to clinical trial tracking systems, and it should be noted that the inputs are likely delayed due to COVID-19. The resulting data only represents a snapshot of the impact from each reporting company. We expect the data and trends to change on a daily basis. ACRO plans to continue to share our data and insights as the current situation evolves.

Institutions Impacted

	14 March	21 March	28 March	6 Apr (week)
Global	10 %	34 %	45 %	49 %
US	4 %	28 %	44 %	47 %
China	45 %	45 %	53 %	57 %
So Korea	86 %	82 %	82 %	69 %
Italy	66 %	79 %	80 %	82 %
Spain	38 %	78 %	80 %	80 %

Broadly defined as any site or institution where patient visits or site monitoring visits have been restricted, rescheduled, postponed, or cancelled due to COVID-19

Visits Cancelled or Delayed vs. Planned

	January	February	March
Global	7 %	8 %	33 %
US	14 %	11 %	35 % (12 % - 57 %)
China	28 % (7 % - 100 %)	69 % (47 % - 100 %)	49 % (35 % - 71 %)
So Korea	1 %	14 %	34% (29 % -38 %)
Italy	6 %	12 %	49 % (34 % - 57 %)
Spain	10 %	5 %	38 % (8 % - 62 %)

Site Inaccessibility & Site Closures

Global
March average: ~35 % sites closed EOM March: ~70 % sites inaccessible
China
Peak crisis: ~80 % sites inaccessible EOM March: ~40 % sites inaccessible ▲

New Subject Study Enrollment:

Year over Year (YoY) Difference between March 2020 and March 2019

By Country	YoY Difference
All Countries, All TAs	-65.1 % ▼
India	-83.9 %
United Kingdom	-80.1 %
France	-68.2 %
Spain	-68.1 %
China	-67.5 %
US	-66.7 %
So Korea	-61.1 %
Italy	-52.3 %
Japan	-43.5 %
Germany	-32.5 %

By TA	YoY Difference
Endocrine	-80.5 %
Cardiovascular	-69.7 %
CNS	-68.5 %
Dermatology	-64.0 %
Oncology	-48.4 %
Infectious Disease	-46.8 %
Respiratory	-33.7 %

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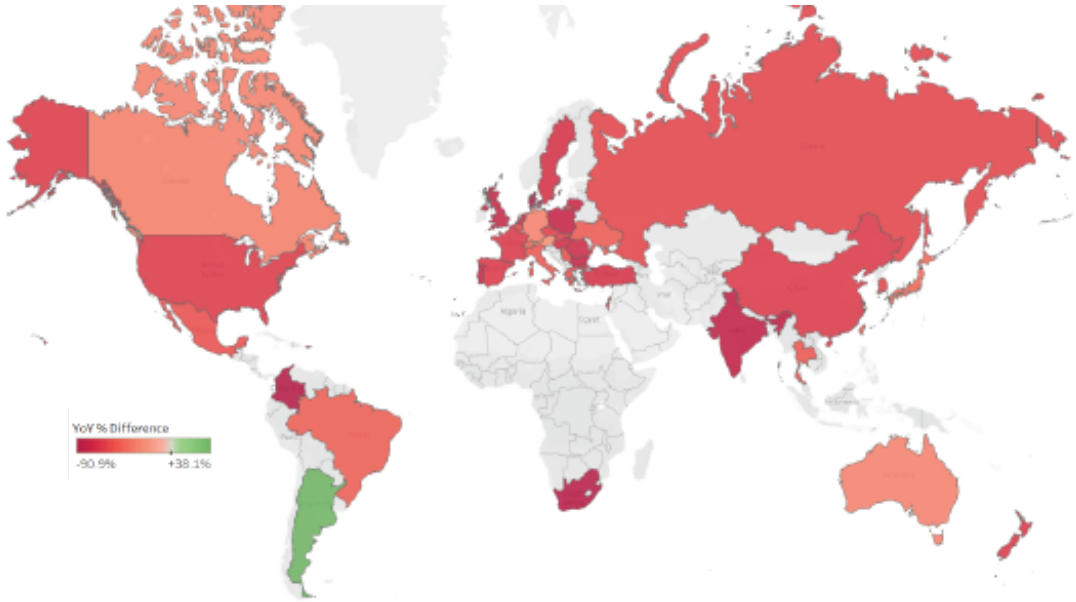
New Subject Study Enrollment (cont).
Heat map: all countries, all TAs, YoY March



New Subject Study Enrollment – February vs. March 2020
Two countries *did* increase the % of new patients added between February and March: China and Argentina

- In China, March was 240% higher than February. This may demonstrate a potential return to normal.

Other Takeaways – Reported by ACRO Member Companies

- 65.1 % decrease in the average number of new patients entering trials per study-site year over year during March. Most geographic regions have been heavily impacted.
- New trial start-up activities have been delayed as a result of site closures.
- The decline in site-based monitoring has been offset by implementation of remote and risk-based monitoring.

Increasing Requests for Remote Access to Source Documents

To ensure alignment with Risk-Based Quality Management (RBQM) as a best practice and to avoid unnecessary burden to sites, ACRO advises against accessing electronic health records remotely, unless the process was already in place. You can read our complete statement, Considerations to Support Clinical Trial Monitoring Oversight During COVID-19, on ACRO's website. Similarly, we suggested that asking sites to fax or upload source documents for remote review places unnecessary burden on sites and creates potential subject data privacy concerns.

Today, ACRO member companies are seeing requests from sponsors for remote access to medical records and other source documents through the following methods:

- Submission of redacted medical records and other source documents in whole or part via email
- Uploading redacted or un-redacted medical records and other source documents in whole or part via document sharing systems (e.g., Box.com, etc.)
- Using video platforms (e.g., WebEx, FaceTime etc.) to have sites film medical records and source documents so that CRAs can monitor the data remotely.

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In many countries, these practices may violate data privacy laws. Further, even if acceptable to some site staff (PIs and coordinators), such practices may be prohibited by institution policies, breach Electronic Health Records (EHR) contractual obligations, and take liberties with IRB/EC approved patient informed consent data privacy statements. In addition, if not previously used at the site for the particular trial, these processes would require confirmation and assessment of chain of custody, data retention and security processes as well as access and permission protocols.

ACRO recognizes that alternative ways of accessing source documents may be warranted under certain circumstances, such as safety reporting or critical endpoint collection in pivotal trials. However, we do not believe that achieving 100% SDR/SDV of endpoints for interim analysis or database lock represents an exigent circumstance that warrants unplanned-for remote access to source documents.

Recommendation: ACRO asks that Regulators articulate a stronger position against the use of remote access to source data for routine vs. critical purposes. Reiteration of support for centralized monitoring and risk-based approaches will help provide confidence in the quality of data already monitored. The EMA took a strong stance against remote SDV in their recent guidance[1] (*see section 11, page 9*). This is an opportunity for RBM to become the "new normal."

[1] European Medicines Agency (EMA): Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic Version 2 (27/03/2020). Section 11: Changes to Monitoring. Page 9. Link: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

Preparation for Post-COVID-19 Resumption

ACRO member companies have started preparations for monitoring clinical trials once the COVID-19 peak has passed. It is paramount that additional attention should be paid to risk evaluation in the post-COVID-19 recovery phase.

As shelter-in-place requirements relax, on-site monitoring activities that have been on pause for a number of weeks or months will resume. We anticipate a large and sudden increase in on-site visits as monitoring resumes across sponsors and trials, including multiple monitors across multiple day visits to assess study status and review subject data backlog. Compounding the risk, sites and site staff may not be back to full capacity and they may still continue to restrict site visitors, including monitors. With multiple sponsors/CROs requesting monitoring visits, we foresee challenges coordinating a return to normal that may further delay monitoring activities and potentially impact subject safety and data quality.

Recommendation: To support investigative sites and assist sponsors/CROs in prioritizing monitoring activities which have greatest impact to participant safety, ACRO is recommending that Regulators provide suggestions on how to prioritize on-site monitoring visits. If industry follows a tiered approach, with the primary emphasis on participant safety, this will help to mitigate an overload at the site-level.

- Tier 1 - High risk and/or potential to directly benefit research participants
- Tier 2 - Moderate risk and/or potential to directly benefit research participants
- Tier 3 - Primarily observational studies without risk and/or potential to directly benefit research participants

Such direction to industry will help to decrease potential risks to subject safety and data quality.

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