Proposing minimum requirements for announcing clinical trial results during the COVID-19 pandemic

Mark J. Siedner MD MPH *1,2,3
Rajesh T. Gandhi, MD 1,3

1Harvard Medical School
2Medical Practice Evaluation Center, Massachusetts General Hospital
3Division of Infectious Diseases, Massachusetts General Hospital

*Corresponding Author
Mark Siedner, MD MPH
100 Cambridge Street, Suite 1600
Boston, MA 02114
Abstract

Recently, results from at least three major randomized clinical trials studying management of COVID-19 have been announced via press release without accompanying information. Given the unique nature of the pandemic, results of such trials often have immediate and worldwide relevance. Yet, while press releases serve the important purpose of disseminating top-level results quickly, they are inherently limited in scope, and rarely include sufficient data to inform practice. Herein, we propose a minimum set of trial characteristics and results to be released simultaneously with clinical trial announcements. This practice will ensure data related to management of COVID-19 can be used to appropriately impact care, while responding to the needs of diverse stakeholders in the scientific and publishing communities, as well as the public at large.
On June 13, a press release rocketed across Twitter, news headlines and the medical community about the first clinical trial demonstrating a mortality benefit for the treatment of COVID-19. Study investigators announced that, “the preliminary results are very clear – dexamethasone reduces the risk of death among patients with severe respiratory complications.” A scattering of data points followed – mortality rates in the control arm, relative risk ratios and confidence intervals demonstrating benefit of dexamethasone in reducing 28-day mortality in certain sub-groups, and a promise to publish the “full details of the data as soon as possible.”

By most accounts this innovative, adaptive design study appears to be a long-awaited victory in the global response to COVID-19 epidemic control. That dexamethasone is a low-cost, generic, and truly globally available therapy raised hopes even further. But shortly after the press release, a question quickly emerged among physicians and clinical trialists and guideline authors about use of dexamethasone in practice for COVID-19: “What now?”

While compelling, the press release lacked crucial data required to assess study limitations or guide use of dexamethasone in clinical practice. Namely, participant demographics to determine generalizability, toxicity data to guide patient monitoring, data to assuage concerns of potential bias due to the open-label design (i.e. were those in the intervention arm more likely to receive intensive care unit transfer or mechanical ventilation), or information about balance within sub-groups (randomization was not stratified by disease severity, yet results were only reported in these stratified sub-groups).

With thousands of deaths attributed to COVID-19 each day globally, the urgency to report potentially practice-changing results from COVID-19 clinical trials is clear and warranted. The investigators were justified in rapidly analyzing and announcing their results. Yet, the traditional rigor of the scientific peer review process was not designed for immediate dissemination of results during public health emergencies, even despite journalistic considerations during these unprecedented times.[1] Moreover, scientific press releases, which are brief by nature and historically susceptible to under-reporting of data,[2] cannot be expected to include a full accounting of study results. But does announcing efficacy point estimates in the absence of other information achieve goals to quickly inform practice? How should such limited data, once available, impact guidelines and current clinical care? What should we tell patients and families who have read press releases and have justifiable questions about optimal treatment of COVID-19?

There are many stakeholders to consider when releasing clinical trial results: the public at large, the scientific community, clinicians, their patients and families, funders, and scientific journals, among others. As an indicator of how much things have changed during the...
COVID-19 epidemic, these stakeholders have previously been more critical of trial investigators and sponsors for releasing clinical trial results too late (or not at all).[3] In contrast, in the current era, the most apparent competing interests related to data availability concern a tradeoff between urgently providing sufficient information to affect clinical care, while not abandoning scientific principles to assure rigor and to address bias and generalizability. But many additional tensions often lurk below the surface. Investigators might refrain from sharing data publicly because many top medical journals historically penalized public dissemination prior to peer review. Such disqualifications can have significant downstream implications. Scientists and pharmaceutical companies often pour decades of work and resources into such studies, and their careers and profitability, respectively, depend on their success. Meanwhile, scientific journals have financing models that rely on subscriptions and advertising which result in pressures to not reveal -- or embargo -- results until they are published.

Ultimately, as the scientific community who lead these trials, we are the stewards of this information, and responsible for the timing, nature, and extent of results communication. But deciding between prompt release of data to impact change and rigorous scientific review is a false dichotomy. For most large clinical trials, a thorough and publicly available study protocol is coupled with analysis by an independent data safety and monitoring board (DSMB). These committees carefully and thoroughly consider benefit, futility, safety, and bias.[4] In short, if investigators feel that primary results meet criteria for public release, information about safety and validity must also necessarily meet these criteria. Releasing the former without the latter creates a public expectation to change medical practice without the necessary tools to do so.

How can we meet the needs of diverse stake holders when presenting time-sensitive trial data? Concurrent with a press release, clinical trial investigators should be encouraged to release a minimum set of accompanying data or results that would respond to stakeholder needs (Table 1), and be consistent with standard of clinical trial reporting.[5] In such a way, investigators and sponsors could simultaneously promote prompt results dissemination, allow clinicians and guideline developers to make informed decisions, and satisfy regulations and expectations of funders and scientific journals. None should preempt subsequent peer-reviewed publication or granting credit to the investigators where it is due. Multiple formats would meet these criteria: 1) updating of the Clinicaltrials.gov or alternate trials registry with preliminary results; 2) public release of the full study protocol and analysis plan with an accompanying de-identified dataset; 3) an impromptu (online) public seminar to include a scientific presentation akin to a medical conference; 4) publication of a pre-print or preliminary results document; 5) publication of the signed and approved data safety monitoring board (DSMB) analysis and report.

The dexamethasone data release was the third example of a major COVID-19 therapeutic randomized trial result announced via press release without accompanying information since late April. In the months that follow, we will welcome many similar advances in the global
response to the COVID-19 pandemic. As they arrive, we as a scientific community have an opportunity to announce victories (and null findings) promptly and thoroughly to meet the needs of our diverse stakeholders, and to be exemplars of transparency and rigor.

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Table 1. Minimum suggested data elements to report at the time of initial public dissemination of clinical trial results

| Data Element              | Minimal Reporting                                                                 | Relevance                                                                                       | Examples for COVID-19 Clinical Trials                                                                 |
|---------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Study design              | - Randomization and arms - Control design - Blinding - Geographic locations - Study timing and duration | Provides context on study quality, strengths, and potential weaknesses                           | - Open-label versus blinded (placebo and/or dummy description) - Components of standard of care - Nature of standard of care - Location and timing to put in context of epidemic trends |
| Participant characteristics| - Sample size in each arm - Sociodemographic characteristics - Comorbidities and clinical characteristics | Required to determine generalizability of study population and patient selection for clinical use | - Age - Sex - Co-morbidities (diabetes, obesity, immunosuppression) - Concurrent therapies (other antiviral agents or immunosuppression) |
| Primary findings          | - Protocol-specified primary outcome including absolute and relevant events and confidence intervals - Major pre-specified secondary outcomes including sub-groups and secondary outcomes are welcome, but not in lieu of the primary outcome in the total study population | Required to determine effect size                                                               | - Depending on protocol, mortality, requirement for mechanical ventilation, duration of disease - If secondary outcomes are reported they should be labeled as such - Sub-group analyses should include interaction terms |
| Toxicity and Safety Data  | - Major adverse events by arm, including deaths - Protocol-specified adverse events | Required for patient monitoring and safety assessments                                            | - For antivirals these should include standard FDA-defined adverse events - For immunosuppressive agents, data on secondary infections should be included |
| Study Limitations         | - Study-dependent                                                                | Permits public and scientific community to understand the scope and potential interpretation concerns | - Generalizability - Issues related to open-label designs - Consideration of balance between randomized arms or in sub-groups |

FDA: Food and drug administration