

# Promoting Better Clinical Trials and Drug Information as Public Health Interventions for the COVID-19 Emergency in Italy

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At the outbreak of the severe acute respiratory syndrome coronavirus 2 epidemic in Italy, non-peer-reviewed articles and press releases of small clinical trials, coupled with the general amplification and uncritical reporting of "potential cures," led physicians to use many drugs off label with high expectations of their potential benefit. This was not unique to Italy, as most countries facing the outbreak encountered similar situations. The Italian Medicines Agency (AIFA) strongly believes that only well-designed randomized clinical trials (RCTs) are able to answer the following question, as recently advocated in many clever commentaries (1-4): Does something work, and how much does it work?

On 17 March 2020, the Italian government established a new law that all clinical trials on coronavirus disease 2019 (COVID-19) treatments should be evaluated by AIFA and, subsequently, by a single research and ethics committee (National Institute for Infectious Diseases Lazzaro Spallanzani) (5). The agency immediately set up an internal COVID-19 task force and capitalized on its scientific committee for the rapid evaluation of all research protocols. As of 21 May 2020, 144 clinical trials had been assessed. Of these, 40 (27.8%) had been approved, 10 (6.9%) had been suspended for further clarifications, 92 (63.9%) had been rejected, and 2 (1.4%) were under evaluation (6). The centralized procedure allowed AIFA to use the clinical trial approval pathway to reinforce the pivotal role played by best available evidence, inform clinical practice, and support the emergency governance.

The AIFA hoped to evaluate tocilizumab in an RCT, but rumors, early reports of individual cases, and subsequent media coverage led to widespread prescribing almost immediately. The manufacturer generously made it available for free, and when AIFA became aware of it a few days later, more than 600 prescriptions had already been filled. Given that an RCT was not feasible in that moment, a pragmatic, single-group, phase 2 study was designed by an independent committee (EudraCT: 2020-001110-38). The study recruited more than 330 patients in less than 24 hours and 2000 patients in 2 weeks, all of whom were enrolled in both prospective and retrospective registers, exemplifying how this drug had become perceived as a therapeutic opportunity. Although this study will provide some clues on efficacy, it probably will not provide a conclusive answer. For this reason, AIFA nudged clinicians and the research community to submit an RCT of tocilizumab versus standard of care (SoC), and this was approved 2 weeks later (EudraCT: 2020-001386-37). Stronger nudging led to the approval of a randomized,

multigroup, adaptive trial comparing SoC with tocilizumab, canakinumab, baricitinib, siltuximab, or methylprednisolone in May. In brief, AIFA accompanied the Italian National Health Service from a chaotic phase with small observational studies to a single national multigroup trial in less than a month.

A second example of transition from emergency management to informative clinical trials is given by chloroquine and lopinavir-ritonavir, which were initially defined as control groups or SoC in most clinical trials. This choice presented at least 2 major disadvantages: It provided patients with therapies of unknown benefit as SoC, and it did not allow the opportunity to estimate the magnitude of efficacy, if any, of the experimental drugs. On the other hand, it was reputed to be ethically acceptable because it meant that patients randomly assigned to the control group would receive the same treatment as patients not entering the trial. However, by adhering to the World Health Organization's Solidarity trial (EudraCT: 2020-001366-11), in which chloroquine and lopinavir-ritonavir were individual experimental groups randomized against SoC, AIFA took a progressive stance that SoC should have been defined as best supportive care. A multigroup trial that compared antiviral treatments (lopinavir-ritonavir, darunavir-cobicistat, favipiravir, and hydroxychloroquine) with no treatment (supportive care only) in nonhospitalized patients who were early in the disease, was a positive evolution of this phase. While new strategies were adopted in the evaluation of proposals, the lockdown measures succeeded in containing the spread of the infection. This could have put the completion of trials at risk. Therefore, AIFA made efforts to promote networks among the principal investigators with similar proposals, pushing researchers into bigger RCTs and avoiding patient leakage in redundant, small trials (7).

While reviewing clinical trial protocols, AIFA and its scientific committee progressively realized that there was a gap in information available to physicians and the lay public, with local guidelines becoming varied across the country: Hydroxychloroquine or lopinavir-ritonavir and their combination became the SoC, while antibiotics (initially azithromycin) or other drugs (low-molecular-weight heparins at different doses) became increasingly popular. To overcome this, for each of these drugs, a 2-page card was devised that included the rationale, what data supported its use with a short methodological analysis, the limits of its use, and safety concerns. These cards are now routinely updated on the AIFA website to guide clinicians to more informed choices. The agency also issued a warning against the routine use of some of these drugs and

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their combinations except in clinical trials, thus bridging clinical studies and clinical practice.

In conclusion, evidence-informed prescribing and clinical trials were beaten off the mark by social media, rumors, and panic in the early phase of the COVID-19 pandemic, triggered by the lack of therapeutic options in the treatment of a rapidly spreading and severe disease. Lessons learned during this difficult emergency from a regulatory perspective were the need to counteract misleading information and define a standard treatment on the basis of preliminary data and uncertain findings to avoid potentially harmful combinations; the importance of nudging the research community toward high-quality, large, informative, multigroup clinical trials; and the need to communicate and routinely update information on the basis of best available evidence on both efficacy and safety data. The agency and its scientific committee tried to integrate these 3 streams of activity promoting pragmatic RCTs and drug information as pillars of the Italian National Health Service to manage a rapidly evolving emergency situation.

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## **APPENDIX: AIFA SCIENTIFIC COMMITTEE AND COVID-19 CRISIS UNIT**

Members of the AIFA Scientific Committee were Antonio Addis, PhD\*; Mauro Biffoni, MD†; Carlo Caltagirone, MD†; Giovambattista De Sarro, MD†; Ida Fortino, PharmD†; Armando Genazzani, MD\*; Nicola Magrini, MD\*; Anna Maria Marata, MD†; Patrizia Popoli, MD†; and Paolo Schincariol, PharmD†.

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