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Commentary

# COVID-19 trials in Italy: A call for simplicity, top standards and global pooling

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ABSTRACT

The novel coronavirus disease, affecting ~9 million people in the past five months and causing >460,000 deaths worldwide, is completely new to mankind. More than 2,000 research projects registered at ClinTrials.gov are aiming at finding effective treatments for rapid transfer to clinical practice. Unfortunately, just few studies have a sufficiently valid design to provide reliable information for clinical practice.

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In Italy - the first western country affected by the pandemia – 35 studies have been approved by the Italian Drug Agency. We here summarise the study protocols and critically appraise their design, assumptions and endpoints. Currently, about one in seven approved Italian studies has a sufficiently valid design to provide reliable information on the benefit/risk profile of the proposed treatment. Because most treatments proposed to date represent nonspecific *repurposing of available compounds, sensational* results cannot be expected; rather, small to moderate possible favourable effects. For this reason, large, simple, randomised trials using highest research standards are advocated. Additionally, systematic descriptions of national protocols may allow global pooling of trial data with common designs.

The novel coronavirus disease (COVID-19) has affected ~9 million people in the past five months, overwhelmed frontline professionals with patient care and risk of infection, and caused over 460,000 deaths worldwide. Less than a year ago, COVID-19 was unknown to man. Over 2,000 research projects registered at ClinTrials.gov are aiming at finding effective preventive or curative treatments for rapid transfer to clinical practice. Authoritative observers, however, have noted flaws in many of these projects, advocating higher research standards [1–4].

In Italy, the first European country affected by COVID-19, the need for research was perceived as very urgent. Appropriately, the Health Ministry simplified bureaucracy by entrusting project evaluation to the Italian Drug Agency (AIFA) and final approval to a single national Ethics Committee. Laudably, transparency was ensured by publication of the approved protocols on AIFA's website [5]. We appraised the 35 studies approved between March 11 and May 22, 2020, assessing design, assumptions, endpoints and sample size (Table 1).

Most Italian studies focus on severe hospitalised COVID-19 patients and on antiviral, anti-inflammatory or antithrombotic treatments. Only a minority deals with outpatients or disease prevention. Twenty-nine (83%) are randomised, but 22 are open label, and more than half of these are susceptible to biased endpoint evaluation. Nineteen of the 29 randomised studies (66%) are small, based on over-optimistic assumptions of benefit, with a high risk of inconclusive results, even for potentially favourable treatments. Six studies (17%) are observational without appropriate control groups. Only 5 (14%) show a sufficiently adequate overall design to provide reliable results for application in clinical practice (Table 1).

Current COVID-19 study drugs represent nonspecific *repurposing of available compounds* [6]. Nonspecific treatments cannot be expected to yield sensational benefits; rather, small to moderate ones. For COVID-19, on the other hand, even small-to-moderate treatment effects leading to even small relative mortality reductions could have an enormous impact on the absolute number of survivors. A reliable demonstration of moderate treatment benefits and of potential subgroup effects (e.g., by age, sex, comorbidities or disease severity) requires testing in thousands of patients. Currently, about 1 in seven approved Italian studies has a sufficiently valid design to provide reliable information on the benefit/risk profile of the proposed treatment.

The European Medicines Agency recently called for adequately sized COVID-19 trials to produce decision-relevant results [7]. A systematic description of all national trials might show overlapping designs across

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**Table 1**
COVID-19 studies approved in Italy up to June 22, 2020.

| Study | Treatment | Patients | Type of study | Blind or Open label | Primary endpoint | Assumption of benefit | Sample size (subjects) | Authors' overall appraisal |
|---|---|---|---|---|---|---|---|---|
| GILEAD GS-US 540-5773 | Remdesevir 5 vs 10 days vs SOC | COVID-19 + Hospitalised SpO2 ≤94% | Randomised | Open | Normal body temperature and SpO2 at 14 days | 45% for 5 day Rx 60% for 10 day Rx | 400 | No control group. Soft endpoint. Optimistic assumption of efficacy. Probably underpowered |
| GILEAD GS-US 540-5774 | Remdesevir 5 vs 10 days vs SOC | COVID-19 + Hospitalised SpO2 ≤94% | Randomised | Open | % discharged at 14 days | 25% increase with Remdesevir | 600 | Intermediate endpoint. Adequately sized |
| TOCIVID | Tocilizumab | COVID-19 + Hospitalised | Observational | | Death at 14 and 30 days | ARR 10% | 330 | No control group |
| Sobi-IMMUNO-101 | Emapalumab vs Anakinra vs SOC | COVID-19 + Hospitalised SpO2 ≤93% Hyperinflammation | Randomised | Open | % without invasive ventilation or ECMO | 60% increase vs SOC | 54 | Optimistic assumption of efficacy. Probably underpowered |
| Sarilumab COVID-19 | Sarilumab vs Placebo | COVID-19 + Hospitalised | Randomised | Double blind | Not reported | Not reported | | |
| RCT-TCZ-COVID-19 | Tocilizumab + SOC vs SOC + Tocilizumab in case of clinical deterioration | COVID-19 + Hospitalised Pneumonia | Randomised | Open | Occurrence of >1: -death -invasive ventilation -respiratory decline | 50% reduction in primary endpoint occurrence | 398 | Optimistic assumption of efficacy. Probably underpowered |
| Tocilizumab 2020-001154-22 | Tocilizumab vs Placebo | COVID-19 + Hospitalised Pneumonia SpO2 ≤93% | Randomised (2:1) | Double blind | Clinical status on a 7-category ordinal scale | 2-day difference between treatment groups in time to >2 category improvement | 330 | Intermediate endpoint |
| Hydro-Stop-- COVID19 Trial | HCQ 400 mg bid vs SOC | COVID-19 + Out-patients | Randomised | Open | Negative test at 8 days | From 15 to 60% (i.e., 400% increase) vs SOC | 216 | Soft endpoint. Optimistic assumption of efficacy. |
| SOLIDARITY WHO | 5 arms: Remdesevir, CQ or HCQ, Lopinavir-Ritonavir, Lopinavir-Ritonavir + Interferon, SOC | COVID-19 + Hospitalised | Randomised adaptive design | Open | In-hospital mortality | 15-20% reduction | >10,000 | Hard endpoint. Adequately sized |
| COLVID 19 | Colchicine vs SOC | COVID-19 + Hospitalised Pneumonia | Randomised | Open | Death or mechanical ventilation or ICU at 1 month | 50% reduction | 308 | Optimistic assumption of efficacy. Probably underpowered |
| ColCOVID19 | Colchicine vs SOC | COVID-19 + Hospitalized Pneumonia | Randomised | Open | Two-category improvement on 7-category scale at 14 days | 50% improvement | 310 | Soft end-point. Optimistic assumption of efficacy. Probably underpowered |
| INHIXACOVID19 | Enoxaparin | COVID-19 + Moderate/severe disease | Observational | | Death at 30 days | Not defined | 100 | No control group. Inconclusive for the primary endpoint |
| BARICIVID-19 | Baricitinib vs SOC | COVID-19 + Hospitalised SpO2 ≤93% | Randomised | Open | Invasive ventilation at 7 and 14 days | 60% reduction | 126 | Optimistic assumption of efficacy. Probably underpowered |
| COPCOV | CQ or HCQ vs Placebo | Healthcare or other frontline workers | Randomised | Double blind | Symptomatic COVID-19 infection Symptom severity | 23% reduction | 40,000 (20,000 in Asia, 20,000 in Europe) | Hard endpoint. Adequately sized |
| COVID-SARI | Sarilumab | COVID-19 + Hospitalised Pneumonia | Observational | | ≥30% decrease in O2 requirement compared to baseline | Not defined | 40 | No control group |

(continued on next page)

**Table 1** (*continued*)

| Study | Treatment | Patients | Type of study | Blind or Open label | Primary endpoint | Assumption of benefit | Sample size (subjects) | Authors' overall appraisal |
|---|---|---|---|---|---|---|---|---|
| X-Covid 19 | Enoxaparin vs SOC | Elevated D-Dimer<br>COVID-19 +<br>Hospitalised | Randomised | Open | Venous thromboembolism | 33% reduction | 2,712 | Adequately sized |
| PROTECT | HCQ vs SOC | *Prevention:* Healthy subjects or workers in contact with COVID-19 pts<br>*Treatment:*<br>COVID-19 +<br>Outpatients | Cluster randomisation (2:1) | Open | *Prevention*: rate of COVID-19 + at 30 days<br>*Treatment*: rate of COVID-19 at 14 days | *Prevention:* 30% reduction<br>*Treatment:*<br>50% improvement | *Prevention:*<br>3,000-4,000<br>*Treatment:*<br>600 | Complex design. Prevention arm: adequately sized.<br>Treatment arm: optimistic assumption of efficacy |
| ESCAPE | Sarilumab vs SOC | COVID-19 +<br>Hospitalised<br>Pneumonia | Randomised (2:1) | Open | Two-category improvement on 7-category scale at 14 days | 37% reduction | 171 | Intermediate endpoint |
| XPORT-CoV-1001 | Selinexor vs SOC | COVID-19 +<br>Hospitalised<br>SpO2 ≤94% | Randomised | Single blind | Time to clinical improvement | 34% reduction | 230 | Intermediate endpoint |
| AMMURAVID | 7 arms: HCQ, HCQ + Tocilizumab, HCQ + Sarilumab, HCQ + Siltuximab, HCQ + Canakinumab, HCQ + Baricitinib, HCQ + Methylprednisolone | COVID-19 +<br>Hospitalised<br>Pneumonia<br>Elevated D-Dimer or hsCRP | Randomised adaptive design | Open | Severe respiratory failure (PaO2/FiO2 <200 mmHg) at day 10 | Not defined | 350 | Exploratory study |
| HS216C17 | Favipiravir vs Placebo | COVID-19 +<br>Pneumonia | Randomised | Double blind | Time to clinical recovery | 56% improvement | 256 | Soft endpoint. Optimistic assumption of efficacy.<br>Probably underpowered |
| FibroCov | Pamrevlumab vs SOC | COVID-19 +<br>Hospitalised<br>Pneumonia<br>Supplemental O2 | Randomised | Open | % not on ventilatory support ≤15 days | 60% improvement | 68 | Optimistic assumption of efficacy.<br>Probably underpowered |
| AZI-RCT-Covid19 | HCQ vs HCQ + Azithromicyn | COVID-19 +<br>Hospitalised<br>Pneumonia<br>SpO2 <93% | Randomised | Open | Clinical recovery at 10 days | 29% improvement | 144 | Probably underpowered |
| CAN-Covid | Canakinumab vs Placebo | COVID-19 +<br>Hospitalised<br>Pneumonia<br>SpO2 ≤93% | Randomised | Double blind | Survival free of invasive ventilation at day 29 | 15% absolute improvement<br>Between 30 to 75% relative risk improvement | 450 | Optimistic assumption of efficacy.<br>Probably underpowered |
| ARCO-Home | 4 arms:<br>Darunavir-Cobicistat, Lopinavir-Ritonavir, Favipiravir, HCQ | COVID-19 +<br>Outpatients | Randomised adaptive design | Open | *Virologic endpoint:*<br>Negative test at 7 days<br>*Clinical endpoint:*<br>% hospitalized at 14 days | *Virologic endpoint*: 100% improvement<br>*Clinical endpoint:*<br>50% improvement | From 175 to 435 | Optimistic assumption of efficacy.<br>Probably underpowered |
| DEFI-IVID 19 | Defibrotide | COVID-19 +<br>Hospitalised<br>Pneumonia<br>SpO2 ≤92% | Observational | | Respiratory-failure rate | 20% reduction | 50 | No control group |
| COMBAT-19 | Mavrilimumab | COVID-19 +<br>Hospitalised<br>Pneumonia<br>SpO2 ≤92%<br>Elevated hsCRP | Randomised | Double blind | % not on O2 supplementation at day 14 | 100% increase | 50 | Optimistic assumption of efficacy.<br>Probably underpowered |
| PRECOV | HCQ | Health professionals<br>COVID-19 negative | Randomised | Open | % with positive test at day 28 | 50% reduction | 1,000 | Optimistic assumption of efficacy |

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|---|---|---|---|---|---|---|---|---|
| DEF-IVID 19 | Defibrotide | COVID-19 +<br>Hospitalised<br>Pneumonia<br>SpO2 ≤92% | Observational | | % respiratory failure rate | 20% reduction | 50 | No control group |
| EMOS-COVID | Enoxaparine low vs high dose | COVID-19 +<br>Hospitalised<br>Pneumonia<br>PaO2/FiO2<250<br>Elevated D-Dimer | Randomized | Open | % mortality or respiratory failure | 33% reduction | 300 | All patients treated with enoxaparine |
| STAUNCH | 3 arms: steroids and unfractionated heparin vs steroids and LMWH vs LMWH alone | COVID-19 +<br>Positive pressure ventilation >24h and<br>invasive mechanical ventilation <96h<br>P/F ratio <150<br>D-dimer and hsCRP >6 x upper limits | Randomised | Open | Death at 28 days | 25% reduction | 210 | Probably underpowered.<br>Very high mortality assumption for LMWH alone |
| TOFACOV-2 | Tofacitinib + HCQ vs HCQ alone | COVID-19 +<br>Hospitalised<br>Interstitial pneumonia | Randomised | Open | % needing mechanical ventilation | 75% reduction | 116 | Optimistic assumption of efficacy.<br>Probably underpowered |
| CHOICE-19 | Colchicine vs SOC | COVID-19 + | Randomised | Open | % hospitalised at 30 days | 50% reduction | 438 | Optimistic assumption of efficacy.<br>Probably underpowered |
| COVID-19 HD | LMWH high vs low dose | COVID-19 +<br>Hospitalised<br>Pneumonia<br>SpO2 ≤93%<br>D-dimer >4 x upper limit | Randomised | Open | In-hospital clinical worsening | 50% reduction | 300 | Optimistic assumption of efficacy.<br>Probably underpowered |
| IVIG/H/Covid-19 | Intravenous polyvalent immunoglobulin | COVID-19 +<br>Hospitalised<br>Pneumonia | Observational | | Survival at 3 and 6 months | Pilot study: not defined | 30 | No control group |

ARR=absolute risk reduction, COVID-19=2019 coronavirus disease, CQ=cloroquine, no.=number, ECMO=extracorporeal membrane oxygenation, hsCRP=high sensitivity C-reactive protein, HCQ=Hydroxychloroquine, ICU=intensive care unit, LMWH= low molecular weight heparin, O2=oxygen, pts=patients, SOC=standard of care, Rx=treatment, SpO2= percutaneous oxygen saturation, vs=versus.

countries that, if valid, might allow pooling of individual patient data. While waiting for an effective vaccine, the crucial question is: will current trial results produce sufficiently reliable evidence on effective and safe preventive/therapeutic approaches to face, potentially next autumn, a relapse of the infection? The answer is hopefully yes, but only thanks to the currently few adequately designed large-scale randomised trials [8–10].

## Author contribution

All authors contributed to the critical evaluation of the studies approved in Italy and to the whole content of the manuscript.

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## Declaration of Competing Interest

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