Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Ideas and Opinions

One year on: The impact of COVID-19 on clinical research

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During COVID-19 epidemic ongoing clinical research slowed down while an unprecedented amount of individual research on the infection broke out disproportionately with results, low respect to the volume of activities. In contrast, all large trials conducted by expert groups adopted on adaptive designs [1–4]. This was new, dictated by the emergency and by the need of finding a way to control the pandemic. Differently from conventional clinical trials, the adaptive designs are flexible and adjustable to the circumstances, even during the course of the study (Table 1) [2]. This is stated by the document on "Adaptive Designs for Clinical Trials of Drugs and Biologics", released by the FDA on November 2019, just before the COVID-19 outbreak: "*the adaptive design allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial*" [5]. There are two key points in the definition. First, the design modifications are possible but must be "*prospectively planned*", i.e. the investigators need to anticipate what aspects of the design could change during the study. The second modifications (adaptations) should be based "*on accumulating data from subjects in the trial*", namely interim analyses performed during the trial. The major concern of the regulators is to preserve the "integrity" of the trial, to avoid that adaptations generate another trial, and to prevent rejecting the null hypothesis by analyzing an ineffective drug, the so-called type 1 error.

1. Running to survive: *to find a drug*

Hundreds of old and new agents were and are investigated in thousands of studies to contrast the Corona virus and its variants. The first was an old drug: dexamethasone, a corticoid to reduce the hyperinflammatory reaction to the infection, which is a major cause of severity of the disease. The drug was beneficial in patients requiring respiratory support (oxygen or ventilation), while failed to improve outcomes in patients with mild disease (RECOVERY trial, NCT04381936) [6]. The interleukin (IL)-6 antagonist tocilizumab, was also shown effective in patients undergoing respiratory support [7]. This was confirmed by the REMAP-CAP trial (NCT02735707) showing a significant reduction in mortality and other secondary endpoints [8]. Other trials have produced controversial results, according to the stage and severity of the disease. The "usual care", on top of which the drugs are tested, may differ within hospitals or even countries included in the trial network, thus a drug may be tested with a different background compromising the consistency of the results. For instance 82% of RECOVERY patients [7] and more than half of REMAP-CAP patients [8] were treated with dexamethasone as "usual care" when tested for tocilizumab, compromising the evaluation of each drug. In a recent metanalysis of 27 RCTs including 10 930 COVID patients the association with mortality compared with usual care or placebo in those receiving corticosteroids were 0.77 (95% CI, 0.68-0.87) for tocilizumab,

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Table 1
General Characteristics of traditional and platform trials* [2].

Charatteristics	Tradizional Trial	Platrform Trial
Scope	Efficacy of a single agent in a homogeneous population	Evaluation efficacy of multiple agents in a heterogeneous population; explicity assumes treatment effects may be heterogeneous
Duration	Finite, based on time required to answer the single primary question	Potentially long-term; as long as there are suitable treatment requiring evaluation.
No. of treatment groups	Prespecified and generally limited.	Multiple treatment groups; the number of treatment groups and the specific treatments may change over time.
Stopping rules	The entire trial may be stopped early for success or futility or harm, based on the apparent efficacy of the single experimental treatment.	Individual treatment groups may be removed from the trial, based on demonstrated efficacy or futility or harm, but the trial continues, perharps with the addition of new experimental treatment (s).
Allocation strategy	Fixed randomization	Response adaptive randomization
Sponsor support	Supported by a single federal or industrial sponsor.	The trial infrastructure may be supported by multiple federal or industrial sponsors or a combination.

*Platform trials and similar trials may also be called basket, bucket, umbrella, or standing trials

confirming the incremental efficacy of the corticosteroid-tocilizumab association compared to steroid alone [9].

Remdesivir, an antiviral drug, is the third agent found effective for COVID-19 patients. An adaptive NIH trial (ACTT1 NCT04280705) showed a significant reduction in time to recovery (11 vs. 15 days) in 1062 patients [10]. This led to its Emergency Use Authorization by the Food and Drug Administration (FDA) in May 2020. The European Medicines Agency (EMA) endorsed the drug later on (November 2020) with conditional approval for hospitalized patients requiring oxygen therapy. The good news was abruptly attenuated by an interim analysis of the adaptive SOLIDARITY trial (NCT04321616) sponsored by the World Health Organization (WHO), showing no benefit in 5451 hospitalized patients [11]. Thus, the WHO released a "conditional recommendation *against* " the use of remdesivir [12]. In mid-February 2021, the Scientific Medical Policy Committee of the American College of Physicians (ACP) refused the WHO's recommendation for "insufficient evidence" and recommended "to onsider" remdevisir's use in hospitalized mild-moderate patients [13]. Studies on remdesivir are still ongoing!

This is almost all we have today. Rather little. It is surprising the lack of effects for drugs acting directly on the virus or its cell penetration and intracellular replication. A further arm of RECOVERY trial testing some artificial antibodies (REGEN-COV2) blocking the penetration of the virus produced promising results. REGEN-COV2 reduced the viral load, and improved outcomes of patients lacking of spontaneous antibodies ("antibody negative") [14]. Let's hope that this approach will be confirmed in ongoing studies.

2. Organized cooperative research: *large simple adaptive trials*

These represent remarkable examples of excellence among the studies with adaptive designs.

One is the already mentioned RECOVERY trial sponsored and managed by Oxford University [15]. As we write, the enrollee's number exceed 40,000 and the tested drugs are 15. Table 2 reports the experimental story of this ongoing trial, which had a major impact worldwide with positive as well as negative results and is an example of the capacity

Table 2
The treatments arms of the RECOVERY trial in approximately one year (March 2020 – March 2021). All enrolled patients (n) were hospitalized. The sample size includes treated and control subjects. Overall approximately 40.000 patients enrolled at May 2001. ClinicalTrials.gov NCT04381936 (last access July 20/ 2021) [24].

Drug	Arm description
Lopinavir-Ritonavir (antiviral)	started March 2020, *ceased* June 2020, n 5040, for *futility*
Hydroxychloroquine (antiviral)	started March 2020, *ceased* June 2020, n 4674, for *futility*
Azithromycin (antibiotic)	started April, 2020, *ceased* November 2020, n 7764, for *futility*
Convalescent plasma (with donor's antibodies)	started May 2020, ceased January 2021, n 10406, for *futility*
Dexamethazone (steroid)	started March 2020, ceased June 2020, n 6424, with *benefit* in severe patients Open to *children only*
Tocilizumab (anti- cytokine 6)	started April 2020, ceased January 2021, n 4116, with *benefit* in severe adults COVID patients. Open to *children only*
Aspirin (anti-inflammatory, anti-platelet aggregation),	started November 2020, n. 15.000, ceased March 2021 for *futility*
Baricitinib (antinflammatory, anti-interleukine 1, antiviral),	started February 2021. *Ongoing*
Colchicine (antinflammatory)	in patients ≥55 years old, started November 2020, n 11.621, ceased Mars 2021 for *futility*
Anakinra (anticitokine 1)	open to children only. *Ongoing*
Biological, intravenous immunoglobulin	Open to children only. *Ongoing*
Dimethyl fumarate (anti-inflammatory, immunomodulator used in psoriasis and multiple sclerosis).	Started February 2021. *Ongoing*
Combination monoclonal antibodies (Casirivimab and imdevimab)	Started September 2020, n 9785, ceased May 2021 for benefit in anti-body negative patients
High-dose desoxycortisone (20 mg 5 days, then 10 mg 5 days)	Ongoing

to integrate research with clinical practice, a goal attempted and frequently not achieved in several countries across the world.

Another remarkable example is the SOLIDARITY trial conducted by the WHO with 48 countries included in the network). The five initial arms testing hydroxychlorokine, Lopinavir-Ritonavir, Interferon beta, Remdesivir and Azytromicine failed [11]. Now, SOLIDARITY explores ways to contrast immune responses. The tested drugs are infliximab, a blocker of the tumour necrosis factor alpha (TNF-α); imatinib an anti-cytokine, and artesunate, an anti-malaric drug with anti-inflammatory effects [16]. Each of these drugs will be given on top of standard care, often including dexamethasone. This new study started on August 6th, 2021

A further trial sponsored and run by Oxford University is the PRINCIPLE trial" (ISRCTN86534580), a platform-based randomized controlled phase 3 adaptive study holding several records [17]. First, it takes place in the *primary care* setting, i.e. through General Practitioners in their practices. Second, it is one of the very first "*virtual*"(pragmatic) trials in the world, i.e. is entirely remote, without any face-to-face visits planned. Third, it recruits older community people (≥65 years, or ≥50 years with comorbidities) showing signs of COVID-19 disease. The first three tested drugs in about 5000 patients- Hydroxychloroquine, Azytromicine and Doxycycline – failed. In January 2021, a further arm was launched on budesonide, an inhaled corticosteroid used in asthma. This arm is already closed for benefit!

3. Organized cooperative research: platforms and networks

The platform scheme for new drug research usually follows a two-phase pathway. The first aims to obtain an early indication of the drug's safety and efficacy in few patients investigated in-depth in

experienced centers. If successful, the drug enters a Master Protocol and advances to a second phase of investigation in large-scale trials, alternatively, it may enter a seamless phase 1-2-3 trial. The trial designs mainly consist in multi-arm models governed by interim analyses. A few examples follow.

1) The ACcelerating COVID-19 Research & Development platform (ACCORD, NCT04280705) brings together a single UK- platform and the UK's leading research expertise (UKRI) [18]. It seems to be an exemplary case of government, industry and research organization. The leading Universities in UK, like Oxford, Cambridge, Southampton, Glasgow, Birmingham, Liverpool, Edinburgh, Manchester and London (each one directing one or more specific lines of research) participate in this medical and social effort. Antiviral, antinflammatory, immunomodulator and antithrombotic drugs are all candidate to be studied. The ACCORD platform runs together with Phase-II drug development platforms: TACTIC (TACTIC-E, NCT04393246, and TACTIC-R, NCT04390464) and CATALYST (ISRCTN40580903).
2) The Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV 1-4 studies, NCT04518410) is sponsored by the NIH. It includes studies on COVID-19 outpatients as the "Adaptive Platform Treatment Trial for Outpatients with COVID-19 (ACTIV 2, NCT04518410)". It is important because the majority of trials have involved hospitalized patients with short follow-up (up to discharge or day 28), whilst the so-called "long COVID" phenomenon (or "post-COVID-19 Syndrome" or "long-haul COVID") is becoming more frequent than initially expected. Patients can have late or mild-moderate symptoms not leading to hospitalization (but exposing other people to the infection), which may last months with frequent psycho-neurological implications just in the US, 15 million cases are expected as sequence of the pandemic [19]. The NIH launched a research program labeled Post-Acute Sequelae of SARS-CoV-2 infection (PASC) with an investment of $1.15 billion over 4 years [20]. To actively face these needs, more than 30 U.S. hospitals and health systems have already opened "multispecialty long Covid clinics" [19].
3) REMAP-CAP COVID (NCT 02735707) is an international randomized embedded multi-factorial adaptive platform phase 4 trial for Community-Acquired Pneumonia. At present, the group is focusing entirely on COVID-19 with more than 250 centers active around the world. As for SOLIDARITY, present targets are immunomodulators, such as the imatinib and namilumab.

An encouraging example of coordinated research within these platforms is the ATTACC Trial, (NCT04372589), spanning five continents with more than 300 hospitals, and testing COVID-19,-prothrombotic risk. Initial results showed that the routine use of full-dose anti-coagulation is not beneficial to critically ill patients but subsequent analysis showed that in moderately-ill hospitalized patients (not in intensive care or receiving organ support) full doses of anticoagulants is safe and better than the routine preventive doses [21].

1) The COVID-19 Clinical Research Coalition represents a group of scientists, physicians, policy makers and funders from over 30 countries - – who promoted a structured response to COVID-19 in poor-resource settings [22]. The main goal aims to take advantage of multinational and multidisciplinary expertise and to run clinical trials in poor-resource area, and help the WHO in its coordinating role for global response to COVID-19".

A "less good" example of absence of reciprocal information and cooperation is the hydroxychloroquine (or chloroquine). "Story" in May 2020, the drug was under investigation in 152 individuals studies involving over 211,000 participants [23]. One month later, 1 June 2020, the trials were 203! Few days later, the hydroxychloroquine arm of hospitalized patients in the RECOVERY trial was stopped for lack of benefit. Immediately afterwards the DSMB of the SOLIDARITY trial performed an interim analysis of their hydroxychloroquine arm plus a meta-analysis of other available data and ceased the arm for futility [11]. The drug was shown to be inactive also in studies performed in outpatients with mild disease and in prophylactic studies [1]. In spite of that, individual studies continued for several months.

4. A glimpse ahead and few conclusions

The pandemic is still far from over, and it is now clear that a Global Vaccination is central to try to avoid the pandemic's perpetual regeneration with new variants. More than 1 billion people has been vaccinated so far, which is a small subset of the world population. In addition, the high proportion of people resistant to vaccination by ideology or fear (about 30% expected in the US [19]) is a concern, together with the difficulties in low income countries. The viral genome is rather unstable. Viruses (as all biological species) naturally mutate particularly during replication, and viruses do replicate continuously. So the frequency of mutations is expected to move on in parallel with the extent of infection across the world. So… most remain to be done. After an attempted universal vaccination, likely incomplete, we will have to accept an endemic COVID-19 reasonably controlled, relatively benign under effective vaccination (available), sensitive to future safe drugs (expected) and prophylactic agents (not at the horizon). A coordinated worldwide research and active monitoring need to be developed with data sharing through an interoperable digital health network. This is the strongest defensive arms the world might oppose to communicable diseases. The European Interoperability Framework recently announced by the European Union might be an important step forward. The availability of deep artificial intelligence will also be of great help.

Authors contributions statement

Each author has contributed substantially and equally to the preparation of this manuscript as follows:

Luigi Tavazzi: conception, design and first draft writing;

Aldo P. Maggioni: critical reading, commenting and contributing to the final version of the paper;

Claudio Rapezzi: critical reading, commenting and contributing to the final version of the paper;

Roberto Ferrari: critical reading, commenting and contributing to the final version of the paper.

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