

Clinical research methodology process: what is changing with COVID-19?

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The repercussions of the pandemic in progress on clinical research have been the systematic interruption of ongoing research and the explosion of fragmented, uncoordinated, often technically insufficient anti-COVID-19 research. Networks of expert centres have emerged setting up well-structured research, adopting much more efficient and aggressive designs than traditional ones. Adaptive designs, characterized by flexibility and mouldability even in the course of studies, which is essential in an epidemic with thousands of simultaneous studies aimed at the same objectives. Some studies are structured with networks of hospitals around guidance centres, such as RECOVERY (Oxford University, UK) and SOLIDARITY (WHO, 30 countries); others with networks of expert centres mostly organized in a combined model: some expert centres test new molecules in Phase 2 in a limited number of patients, and orient promising ones towards connected networks for Phase 3. Cortisones and tentatively cytokines are acquired in the official recommendation. Another emerging model is the pragmatic trial, also called, more expressively, 'remote' or 'virtual'. So it is in fact: the web replaces the direct link between patients and doctors/research operators (CROs included), behind which there will be omnipresent big-techs.

Scientific research in the first year of the pandemic

We are navigating the uncertainty of an unresolved viral pandemic with a double handicap acquired in the last year: the evidence of a global unpreparedness to co-ordinate a lethal infectious risk and the need not to sink into an unmanageable economic and social crisis. The global upheaval caused by the pandemic has also revolutionized clinical scientific research, paralyzing ongoing research, throttled by lockdowns, social restrictions, overcrowded hospitals seen as sources of infection, immersed in a reality that has caught everyone unprepared and medicine literally helpless. In this context, conventional randomized trials disappeared. In April 2021, ClinicalTrials.gov reported the registered suspension of 1773 studies, mainly for COVID-19. In truth, a similar end was predicted as imminent by Milton Packer a couple of years ago,¹ obviously not

following a tragedy like the one in progress, but due to a process of natural death by consumption, favoured by the saturation of the clinical research system.

In reality, the process of traditional clinical research has already been done many times with a set of conventional criticisms, mostly true: huge studies for small objectives with rigid designs, duration and number defined *a priori* (event-driven), slow, cumbersome, and increasingly expensive. Mostly funded by companies, and managed by CROs. Pathophysiological areas that can be explored are limited by costs and the availability of time and interest of researchers, more and more neutral operators not involved in the cultural process that a trial should explore and mostly composite endpoints with subsidiary driving components. Trials are often conducted in non-representative populations, especially today in the face of the possibility of increasing geographical extensions of the use of drugs, without checking in often non-predefined subgroups, typically the co-morbidities, which in large trials correspond to names clicked as patient-reported without any verification or in-depth analysis.

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This worn-out and manifestly awkward status in the reality of the moment was replaced by an instant multiplication of individual studies conducted by single centres or by few occasionally associated centres. The vast majority of this kind of studies, did not lead to anything: repetitive studies, methodologically insufficient, inadequate in number also because they were exposed to local epidemiological variations, above all completely uncoordinated. An example for all. A drug surprisingly favoured by world research in the first months of the epidemic was hydroxychloroquine (or chloroquine). On 1 May 2020, hydroxychloroquine was tested in 152 studies which globally included 211 000 patients.² A month later, on June 1, the hydroxychloroquine trials registered on ClinicalTrials.gov had increased to 203. Four days later, the hydroxychloroquine arm of the RECOVERY trial (NCT04381936), the most important study conducted during this season of clinical research, was discontinued for lack of benefit. Two weeks later, the Steering Committee of the SOLIDARITY trial, (NCT04321616) run by the World Health Organization (WHO), after an interim analysis of its hydroxychloroquine arm came to the same conclusion and stopped enrolment for futility. Moreover, the drug has also been shown to be ineffective in studies conducted in non-hospitalized patients with milder disease and in preventive studies both before and after exposure to the virus.² Despite this, many studies still appeared to be ongoing months after these events.

In contrast networks of centres are rapidly structured at national level by expert researchers with the support of public funding, foundations, charities or companies, or from pre-existing international networks reoriented towards COVID-19. Methodologically, some approaches emerged mostly dictated by urgency. Among these, the adaptive model was absolutely a priority, developed both in network trials with a single co-ordinating centre, and with a combined model consisting of some expert centres that test new molecules in a limited number of patients to verify their potential usefulness and safety as drugs, discarded if unsatisfactory or if promising oriented towards connected networks to enter Master Protocols for larger investigations. Furthermore, the combination of the need to limit interpersonal relationships, including doctors and patients, together with the interruption of physical communications between different places, has led to a sudden rise of digital interactions and the use of the shipment of monitoring and interventional devices or the dispatch of drugs. These were the embryo of current pragmatic trials. Randomization was preserved in all minimally structured studies.

The guidelines after the conversion of the research

Adaptive designs

Adaptive study designs are based on completely different principles from conventional ones. Both are summarized comparatively in [Table 1](#).³ From these principles dozens of trial designs were born, which in the end partially confused the matter. However, the most common practice has been

and is the simultaneous activation in each trial of various randomization arms of COVID patients allocated to different drugs tested against placebo. It is difficult to predict in the protocol the number and timing of the study for each drug, for the simple reason that the response to each new therapeutic agent is unknown. Each arm of the study has its own story. Clinical observation and periodic interim analysis of the collected data guide the Patient Safety Committee (DSMB) and the Steering Committee of the study on how to proceed with the study in relation to that drug. When the results of an arm appear clinically and statistically convincing for the efficacy or ineffectiveness of a drug, that arm is interrupted and another drug enters the evaluation.

To fully define the adaptive model, it may be useful to recall the definition given by the FDA, in November 2019, in an important document entitled *Adaptive Designs for Clinical Trials of Drugs and Biologics* published just a few months before the pandemic outbreak.⁴ The key point of the definition is the following: *the adaptive design allows for prospectively planned modifications to one or more aspects of the design* (also substantial aspects such as sample size, endpoints, treatment arms, dosages of the drugs tested, the duration of the study can be modified) *based on accumulating data from subjects in the trial*. This flexibility can be essential in a pandemic situation with many simultaneous studies focusing on similar objectives. However, the regulatory bodies do not lose sight of a key point, which is the integrity of the study. First of all, the adaptations must not change the nature of the study (in practice by designing another study); moreover, the risk of rejecting the null hypothesis in the analysis of an ineffective drug must be prevented. Thus, in this contest, two fundamental clarifications of the definition must be considered. First, the possible modifications of the study design must be foreseen in the protocol (*prospectively planned*) and will be adopted if the foreseen conditions are met. Second, their application must be based on data emerged in interim analysis of the study data (*based on accumulating data from subjects in the trial*).

As mentioned, some adaptive studies are organized with a coordinating centre that developed the design and manages the study. An example is the Randomized Evaluation of COvid-19 thERapY (NCT04381936) RECOVERY trial conducted by the University of Oxford to which hospitals across the compact UK have joined (3 months after the start of the study 12 000 COVID patients had already been enrolled). Today (May 2021) the number of enrolled patients in the UK exceeds 40 000. [Table 2](#) shows the sequence of drugs tested in just over a year in the RECOVERY. At least four drugs were tested simultaneously, with interim analyses conducted frequently in order to verify any results achieved or, more frequently, evidence of futility reached. Many failures, some partial successes. One is the evidence of the efficacy of dexamethasone in severely ill patients.⁶ A cortisone is obviously not an antiviral drug, it is anti-inflammatory, and these data have confirmed how lethal the inflammatory response to the virus can be in some subjects even when the presence of the virus in the body is now reduced, but the cytokine cascade is triggered. Another anti-inflammatory drug that emerged from the

Table 1 General characteristics of traditional or platform trials³

Characteristics	Traditional trial	Platform trial
Scope	Efficacy of a single agent in a homogeneous population	Evaluation efficacy of multiple agents in a heterogeneous population; explicitly 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.
Number of treatment groups	Pre-specified 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, perhaps with the addition of new experimental treatment(s).
Allocation strategy	Fixed randomization	Response adaptive randomization
Sponsor support	Supported by a single public or industrial sponsor.	The trial infrastructure may be supported by multiple public or industrial sponsors or a combination.

Table 2 RECOVERY treatment groups in about 1 year (March 2020-March 2021)

Drug	Arm description
Lopinavir-Ritonavir (antiviral)	Started March 2020, <i>ceased</i> June 2020, <i>n</i> 5040, for <i>futility</i>
Hydroxychloroquine (antiviral)	Started March 2020, <i>ceased</i> June 2020, <i>n</i> 4674, for <i>futility</i>
Azithromycin (antibiotic)	Started April, 2020, <i>ceased</i> November 2020, <i>n</i> 7764, for <i>futility</i>
Convalescent plasma (with donor's antibodies)	Started May 2020, <i>ceased</i> January 2021, <i>n</i> 10 406, for <i>futility</i>
Dexamethazone (steroid)	Started March 2020, <i>ceased</i> June 2020, <i>n</i> 6424, with <i>benefit</i> in severe patients Open to <i>children only</i>
Tocilizumab (anti-cytokine 6)	Started April 2020, <i>ceased</i> January 2021, <i>n</i> 4116, with <i>benefit</i> in severe adults COVID patients. Open to <i>children only</i>
Aspirin (anti-inflammatory, anti-platelet aggregation), Baricitinib (anti-inflammatory, anti-interleukin 1, antiviral), Colchicine (anti-inflammatory)	Started November 2020, <i>n</i> 15 000, <i>ceased</i> March 2021 for <i>futility</i> Started February 2021. <i>Ongoing</i> In patients ≥ 55 years old, started November 2020, <i>n</i> 11 621, <i>ceased</i> Mars 2021 for <i>futility</i>
Anakinra (anticytokine 1)	Open to children only. <i>Ongoing</i>
Biological, intravenous immunoglobulin	Open to children only. <i>Ongoing</i>
Dimethyl fumarate (anti-inflammatory, immunomodulator used in psoriasis and multiple sclerosis)	Started February 2021. <i>Ongoing</i>
Synthetic neutralizing antibodies (REGN-COV2) (antiviral) ⁵	Started in September 2020, <i>n</i> 9785, <i>ceased</i> May 2021, for <i>benefit on mortality</i> in antibody negative patients at baseline.
High-dose (20 mg 5 days, then 10 mg 5 days) vs. standard desoxycortisone	Started February 2021. <i>Ongoing</i>
Empagliflozin (an SGLT2 inhibitor used in type 2 diabetes and in CV disease)	Started July 2021. <i>Ongoing</i>

All enrolled patients (*n*) were hospitalized. The sample includes both drug-treated subjects and in the control arm. Overall, around 40 000 patients were enrolled in May 2021.

RECOVERY research is tocilizumab,⁷ an antileukotriene six drug (a cytokine), which has given inconsistent responses in other studies. However, beneficial effects were convincingly confirmed in a further large trial⁸ and in a recent meta-analysis of 27 COVID-19 trials.⁹

Another factor to mention in the context of the typology of large and simple trials with adaptive design is

SOLIDARITY, conducted by the World Health Organization (WHO) in 48 countries that have collaborated by enrolling about 12 000 patients. Unfortunately, there have been no positive results so far. Of the drugs tested simultaneously according to an adaptive design: remdesivir, hydroxychloroquine, lopinavir and interferon beta, the mortality at 28 days (primary endpoint) was comparable in the treated

patients and in the controls.¹⁰ Immuno-modulators are now being tested: infliximab, a blocker of tumour necrosis factor alpha (TNF- α), imatinib, an anticytokinetic, and artesunate, an antimalarial drug with potential anti-inflammatory effects.¹¹

One of the experimental results of SOLIDARITY created a serious problem of inconsistency with a drug—remdesivir—an antiviral agent already experimented with little success in previous Coronavirus outbreaks, which had shown efficacy in the first major adaptive trial, the Adaptive COVID Treatment trial (ACTT NCT04280705),¹² well designed and conducted by the US National Institute of Allergy and Infectious Diseases (NIAID), a branch of the NIH. The main result of the trial performed in 1062 hospitalized COVID patients was a significant reduction of the recovery time from the disease: 15 days in controls and 11 days in treated patients. This endpoint was not the only one and it is not among the most solid. Recovery time (essentially hospital discharge) in times of pandemics can be affected by many components other than the effect of the drug tested, and mortality (another primary endpoint) was not significantly reduced, although a favourable trend for the drug was observed. In fact, this was the first glimmer of optimism that appeared from the scientific horizon, with politics waiting for nothing more to try to quell growing anxiety in the population and take time to wait for more convincing results. It is necessary to add that a ‘scientific competition’ was now underway between countries to be able to identify effective treatments in a dramatic epidemiological context that was emerging as one of the most dramatic epidemics in history, which claimed daily tens of thousands of lives.

In short, the story unfolded as follows. Following the results of the ACTT trial, the Food and Drug Administration (FDA) in May 2020 authorized the use of remdesivir for the treatment of COVID-19 patients ‘in emergency’, confirmed in August outside the emergency, finally approved for use in adult and paediatric patients hospitalized for COVID-19 in October 2020. The European Medicines Agency (EMA), more cautiously, issued a conditional approval to use the drug for hospitalized COVID patients with a need for oxygen support in the November 2020. At this point, the Steering Committee of the SOLIDARITY trial in an ongoing interim analysis of its remdesivir arm involving 2743 hospitalized COVID patients and 2708 controls (5 times more numerous than the NIH ACTT trial) interrupted enrolment in the remdesivir arm for absence of benefit (mortality in the remdesivir and control groups was 301 and 303, respectively). Based on these results and a meta-analysis of four trials (including both SOLIDARITY and ACTT) showing neutral results (odds ratio 0.95, 95% confidence interval 0.81–1.11),¹³ WHO issued a ‘conditional recommendation *against*’ the administration of remdesivir in addition to the usual care of COVID patients.¹³ In mid-February 2021, the Scientific Medical Policy Committee of the American College of Physicians (ACP) published an *updated Practice Point on use of remdesivir for COVID-19 treatment* based on a systematic literature review including five clinical trials (one more than those considered in the previous WHO meta-analysis) totalling 7797 hospitalized patients. The ACP explicitly rejected the recommendation of the WHO against the routine use of remdesivir based on evidence

deemed ‘insufficient’¹⁴ and, conversely, recommended to ‘consider’ 5 days of remdesivir treatment in hospitalized patients with moderate COVID-19, extendable to 10 days in patients who have not experienced side effects. Various trials on remdesivir are still in progress at the time of writing (July 2021). Obviously, these inconsistencies in the results of trials conducted in a supposedly technically flawless manner by professional structures, in situations of serious global emergency risk disintegrating the credibility of science and medicine in particular.

Composite adaptive designs

Another structural formula of adaptive trials widely used in the past pandemic year is more composite, it concerns cooperative research organized in platforms with common but operationally independent objectives, nationally, or internationally. We only mention them.

- (1) One is British, the ACcelerating COVID-19 Research & Development platform (ACCORD, NCT04280705), manages a Phase 2 trial of potential anti-COVID-19 drugs including numerous intensive care units in exploratory paths that also can follow one another in continuity in Phase 3 (seamless). It is an example of agreements between government, industry, and research institutes. Universities, such as Oxford, Cambridge, Southampton, Glasgow, Birmingham, Liverpool, Edinburgh, Manchester, and London, participate in this cooperative medical and social effort, each responsible for one or more lines of research in the context of the platform. The Phase 2 TACTIC (NCT04393246) and CATALYST (ISRCTN4 0580903) studies are conducted in close alliance with the ACCORD platform.
- (2) A similar collaborative scenario has developed in the USA with Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV 1-4 studies, NCT04518410). In April 2020, the NIH announced the public-private partnership ACTIV covering four areas of Fast Track Research. An important aspect of the vision of ACTIV is the attention to patients who are no longer hospitalized. An important limitation of all COVID clinical research was the concentration on the acute phase of the infection, for which the follow-up ended almost systematically with hospital discharge or at the canonical 28th day. Today it is clear that the infection is systemic and its consequences over time are frequent and can become significant. The Adaptive Platform Treatment Trial for Outpatients with COVID-19 (ACTIV 2, NCT04518410) is an example.
- (3) REMAP-CAP COVID (NCT02735707) is an international adaptive platform for Phase 4 randomized trials founded ~20 years ago to treat Community-Acquired Pneumonia. It is a clinical platform aimed at the continuity of experience and cultural improvement (continuous learning) regarding a widespread disease, particularly in poor countries. It has about 250 connected centres around the world and is now entirely focused on COVID-19. Doctors have

Table 3 Remotely proposed adaptations of randomized trials¹⁷

Proposed remote adaptation ^a	Considerations potentially affecting trial integrity
Obtaining informed consent	
Mailed or web-based	<ul style="list-style-type: none"> • Cannot observe or witness signature • May not facilitate staff assessment of the participant's comprehension and understanding
Video	<ul style="list-style-type: none"> • Participant must have and be able to use video equipment at home • Distractions at home may interfere with the informed consent process • Developing a strong connection with study personnel may be more difficult by video
Remote outcome measures	
Video instructions and coaching while self-administering	<ul style="list-style-type: none"> • Settings differ between homes, such as availability of an unobstructed walking course, differences in height of chair for standing tests • Balance testing may not be safe
Self-administered without supervision	<ul style="list-style-type: none"> • Without supervision, the quality of collection is unknown • Household members may help or substitute for the participant • The participant may forget or may not bother to perform the measure • Additional burden on participant
Data collection at a participant's home	<ul style="list-style-type: none"> • Travelling to participant's home requires time and may be more costly than having the participant come to the medical centre • Home environments differ and could affect standardization of some data collection methods • Some outcomes requiring sophisticated equipment may not be appropriate for home collection
Interventions	
Study pills mailed or delivered	<ul style="list-style-type: none"> • Relies on mail delivery, which can be problematic particularly in rural areas • Requires participant to return bottles if pill counting is used for adherence
Behavioural interventions	<ul style="list-style-type: none"> • Some evidence suggests that in-person behavioural intervention is more potent than remote

^aEach remote aspect of clinical trials has advantages that include greater convenience by eliminating the time, effort, and resources required for participant travel to a medical centre and potentially facilitating participation by individuals living far from medical centres or who have disabling medical conditions that make travel particularly difficult.

a list of 20-30 drugs from which they can choose, with the help of some supporting notes, the one that seems most suitable for the specific patient. The platform is currently involved in the study of antiviral agents, corticosteroids, and immunoglobulins.

- (4) A final example concerns the AntiThrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC Trial, NCT04372589). One of the aspects that emerged from the COVID-19 experience was the high incidence of widespread macro- and micro-thrombotic complications. Three trials of anticoagulants (ACTIV-4a, ATTACC, and REMAP-CAP) were designed with the aim of sharing the data under analysis.¹⁵ A network of more than 300 hospitals participated in the study and gave conclusive results within months. The first finding was that the routine use of full-dose anticoagulation was not useful in critically ill COVID-19 patients and could be dangerous in some. The second, in hospitalized patients with moderate COVID-19 (non-intensive care unit) full doses of anticoagulant were safe and more effective than the usual preventive

anticoagulant doses. A subsequent study conducted in Brazil on 19 615 COVID patients distinguishing different subgroups based on the clinical status and the dosage of the various anticoagulants used (ACTION trial) produced less clear results for clinical transposition.¹⁶

PRAGMATIC trials

This randomized trial design is also not new; numerous trials claiming to be pragmatic are published. However, the term can be used to express different concepts. One is the practical trial, which some people view as historical trials with linear, simple protocols around a defined goal, clinically important, non-redundant datasets, careful protocol management, with a lot of attention to the few endpoints and follow-up times. Contemporary examples of large, simple randomized trials are most of those reported above, with the peculiarity that the trial designs were adaptive in relation to the emergency situation. Another thing is the 'remote or virtual' trial which today is also called pragmatic (and Next-Gen Clinical Trial).¹⁷⁻¹⁹

In practice, the relationship between patients, investigators, and the co-ordination structure is reduced to a minimum, replaced by the web. The patient receives an invitation, a description of the few practices necessary for enrolment, including informed consent. No visits or contact with living people. If enrolled, he will receive information on the drug to be tested consistent with its allocation in the trial, the drugs to be taken, methods and timing of re-contacts, and follow-up cards. The visits, if there will be one, will be done remotely. The collection of physical data will be achieved with appropriate telemetry methods. It must be said that electrocardiography, cardiovascular, and ultrasound of each body district, spirometry, polysomnography, exercise capacity, the same neuropsychological tests can be obtained remotely and obviously these technological products will multiply rapidly (Table 3).¹⁷ Clinical events, including hospital admissions, and endpoints generally will be recorded in the electronic patient record (EHR) and from there will converge into the study database. It follows that these studies are taking place only in countries where the Health System incorporates the EHR system in which everyone's health life is transcribed (in perspective, our Fascicolo Sanitario—Health Record). Some trials concluded and those in progress are highly visible in the literature and in international conferences. By way of example, one is the SPIRRIT-HFpEF trial (NCT02901184) conducted in Sweden by the University of Uppsala (the Karolinska Institute) with the collaboration of Duke University and the NIH. It is a registry-randomized trial, a model trial already successfully conducted in Sweden. It is open, in progress since 2016 and will end in 2022 with the enrolment of 3200 patients with heart failure and preserved EF (ejection fraction), randomized to spironolactone (generic, the trial is not corporate) vs. placebo (650 patients will be enrolled in the USA). Importantly, the hospitalization endpoints for heart failure and cardiovascular death of Swedish patients are obtained from the respective well-established national registries.

Among the trials concluded, one, very popular, deserves to be mentioned. It is the ADAPTABLE trial (nothing to do with the Adaptive model) conducted in the USA (NCT02697916). The goal was to establish 'definitively' (as it is written in the protocol) the most effective and safe dosage of aspirin in patients with documented atherosclerosis. From the EHR archive 450 000 people corresponding to the inclusion criteria; including aspirin intake; were identified, and invited to participate in the study. Fifteen thousand individuals from 40 clinical centres were enrolled and were randomized to take either 81 mg or 375 mg of aspirin per day. The trial was open, so the patients were informed of and consented to the modification of the therapy. The patients' current therapy before enrolment included aspirin 81 mg in 82% of cases and 375 mg in 7%. At the end of 4 years of follow-up (median 2 years), the incidence of cardiovascular events was identical in the two groups, but it was found that 42% of patients randomized to 375 mg had taken 81 mg of aspirin per day and 7% of those randomized to 81 mg had taken 375 mg. Furthermore, these crossovers had occurred largely in the first 2-3 weeks after enrolment.²⁰

The extraordinary aspect of this failed study is that it was presented as the first very large trial experienced by PCORnet, a platform that includes 70 million Americans and the most prestigious universities in the country, whose mission is summed up in one simple sentence: 'To conduct patient-centred and data-enabled clinical research to deliver results that matter, faster', with a network designed to conduct 'real-world evidence studies, pragmatic clinical trials, population health research, health systems research, and studies on how best to engage patients in research'.²¹

The obvious sticking point of the ADAPTABLE, which explored the best dosage of aspirin, was patients' adherence to the assigned dose, probably best achievable with the blind study, explicitly avoided by the Steering Committee to interfere as little as possible on the patient's habits (*to minimize the challenge of translating trial findings into clinical practice*), which many of the patients in fact kept.²¹

Most of the pragmatic trials done so far have aimed at categorical answers to the question the trial set out to answer: yes or no, this or that. It is the area of clinical research to which remote trials can best lend themselves. It is foreseeable that the very low costs, the short times, the organizational agility constitute a strong temptation to categorize every clinical question, but in most cases, this would be rudimentary, misleading, and very far from precision medicine. It will be necessary to use culture and common sense. As always, however.

In the pragmatic trials done so far, randomization has remained central to the study design. It is the only unchanged feature.

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