Clinical research methodology process: what has changed with COVID-19?

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The immediate repercussions of the pandemic on clinical research were the systematic interruption of ongoing studies and the explosion of tens of thousands of anti-COVID-19 research protocols reported in fragmented, uncoordinated, often technically insufficient international registers, from which almost nothing of significance was produced. In the first two years of intensive research, anti-inflammatory and anticoagulant benefits were identified, while the systemic nature of the viral disease was clearly manifested, but no specific antiviral drugs emerged. Subsequently, monoclonal antibodies and antiviral drugs such as Ritonavir-Boosted Nirmatrelvir (Paxlovid) have given way to more specific therapies, even if surprisingly little used. Finally, the new national Electronic Health Record (EHR-FSE2 Fascicolo Sanitario Elettronico 2 in Italian) was approved as a law, which will integrate the previous one, which is in fact not functional. The systematic, orderly and complete collection of the health data of each citizen constitutes a radical modification of the current National Health System, epidemiology and clinical research.

Scientific research in the early part of the pandemic

We are still navigating in the uncertainty of an unresolved viral pandemic with a double acquired handicap, immediately evident: a global unpreparedness to coordinate a lethal infectious risk, and the need not to sink into an unmanageable economic and social crisis. In the third year of the pandemic, a war has been added in Europe which is in danger of turning into a disaster without borders, generating, as a side effect, a world food crisis due to a shortage of wheat, which cannot be exported from the militarily involved areas, among the of world most important producers.

In this context of insecurity and instability, clinical scientific research has also been upset. In April 2021, ClinicalTrials.gov reported the suspension of 1773 registered studies. In reality, the process of revision of traditional clinical research has already been done many times with a set of conventional but mostly true criticisms: large studies for small objectives, which mainly interest those who pay them, with rigid designs, duration and numbers defined a priori, slow, cumbersome, and increasingly expensive. Mostly funded by companies, and managed by CRO (Contract Research Organization). Trials conducted in populations that are not always representative, especially today in the face of the growing geographic extension of the recruitment networks, with mostly composite endpoints with subsidiary driving components and neutral operators, not involved in the cultural process that a trial should instead activate.

This worn-out and manifestly impractical reality in the aggressive reality of the moment was replaced by some networks of centres rapidly structured at national level by expert researchers with the support of public funding, Foundations, Charities, or companies, or by pre-existing international networks refocused on COVID-19.

Methodologically, some approaches also emerged dictated by the context of a Medicine devoid of appropriate resources. These include the adaptive model that was

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initially a priority, and the pragmatic model that accom-
panied it later. We will go through them quickly. Fur-
thermore, the combination of the need to limit inter-
personal relationships, the frequent impenetrability of
hospitals together with the blocking of physical com-
mu nications between different places has led to the use
of telemetry and an intensification of relationships via
e-mail for both exchange of information, sending of
drugs, or devices up to virtual visits. The embryo of cur-
rent pragmatic trials, randomization, was maintained in
all minimally structured studies.

Clinical research is reorienting

Adaptive designs

The designs of adaptive studies are based on completely
different principles from conventional ones. Both are
summarized comparatively in Table 1. From these prin-
ciples, dozens of designs were born, which in the end
partially confused the matter. However, the general pro-
file of the design can develop both in network trials with
a single coordinating centre, and with a combined model
consisting of some expert centers that test new mole-
cules or new applications of known drugs in a limited
number of selected patients, verify their potential utility
and safety, and if promising they orient them towards
connected networks that insert them in Master Protocols
and test them in adequate real-world cases. Each arm of
the trial has its own history, oriented by clinical
observation and periodic interim analysis of the col-
lected data. The drug found to be effective becomes part
of the recommended therapy or usual care, and is then
used in all subsequent patients enrolled, including con-
trols. To give an idea of the versatility of the adaptive
model, we can recall two widely used designs, very dif-
ferent from each other. One is the so-called ‘umbrella’,
aimed at the simultaneous comparative verification of
various drugs, allocated in distinct arms of the trial,
against a disease. For example, COVID-19.

The other is the ‘basket’, in which a drug with specific
characteristics against a pathophysiological process is
used in patients with different diseases that more or
less significantly involve the activation of that process.
For example, inflammation. To fully understand the
adaptive methodology, it may be useful to recall the de-
finition given by the FDA, in November 2019, in an im-
portant document entitled ‘Adaptive Designs for Clinical
Trials of Drugs and Biologics’ published just a few months
before the outbreak of the pandemic. The key point of
the definition is the following: ‘the adaptive design al-

dows for prospectively planned modifications based on
accumulating data from subjects in the trial to one or
more aspects of the design’. (Substantial aspects of the
trial design such as sample size, endpoints, treatment
arms, drug dosages tested, and study duration may also
be modified.)

Thus the adaptive model is flexible, an essential qual-
ity in a pandemic situation with many simultaneous stud-
ies centred on similar objectives. However, the regula-
tory bodies do not lose sight of a key point: the
integrity of the study. First of all, the possible modifica-
tions of the design must be foreseen in the protocol
(‘prospectively planned’), motivated by the forecast of
different possible evolutions of the study and applicable
if these occur. In addition, the variation of the design
must be based on data emerged in interim analyses of
the study (‘based on accumulating data from subjects
in the trial’).

| Characteristic | Traditional trials | Platform Trial |
|---------------|-------------------|----------------|
| Aim           | Efficacy of a single agent in a homogeneous population | Evaluating the effectiveness of multiple agents in a heterogeneous population |
| Duration      | Fixed, based on the time required to answer the single primary question | Potentially long-term, as long as there are suitable treatments that require evaluation |
| Number of treatment groups | Pre-specified and generally limited | Multiple treatment groups; the number of treatment groups and specific treatments may change over time |
| Interruption rules | The entire trial can be terminated early for success, futility or danger, based on the apparent effectiveness of the single experimental treatment | Individual treatment groups can be removed from the trial, based on proven efficacy, futility or danger, and the trial continues with the addition of new experimental treatments |
| Assignment strategy | Pre-established randomization | Modular randomization based on the response |
| Sponsor support | Supported by a single public or industrial sponsor | The trial infrastructure can be supported by multiple public, industrial sponsors or a combination of the two. |
As mentioned, some adaptive studies are organized with a coordinating centre that develops the design and manages the study. An example is the Randomized Evaluation of COVID-19 Therapeutic Interventions and Vaccines (trial ACTIV-1, ACTIV-2, NCT04518410). In April 2020, the NIAID (NIH) announced the public-private partnership ACTIV covering four areas of Fast Track Research. It is a randomized, controlled phase II and III platform trial that evaluated and evaluates drugs active on the immune response or in the control of viral activity. An important aspect of the ACTIV perspective is the attention to patients who are not or 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 long-term consequences are frequent and can become significant. The ‘Adaptive Platform Treatment Trial for Outpatients with COVID-19’ (ACTIV 2) is an example.

REMAP-CAP (NCT02735707) (Randomized, Embedded, Multi-factorial, Adaptive Platform trial for Community-Acquired Pneumonia) is an international adaptive platform for phase 4 randomized trials founded about 20 years ago to treat Community-Acquired Pneumonia. It is made up of about 250 connected centres around the world. Doctors have 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. The REMAP-CAP COVID is a sub-platform entirely dedicated to COVID-19 operating in the USA.

A final example concerns the AntiThrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC Trial, NCT04372589). Atypical study, actually a merger of three distinct anticoagulant studies (ATTACC, ACTIV-4a, and REMAP-CAP) motivated by the high incidence of widespread macro- and micro-thrombotic complications observed in COVID-19 and designed with the aim of sharing data in Bayesian analysis.

**Virtual trials (pragmatics) (Table 1)**

Numerous trials are published that claim to be pragmatic and revolutionary, but this randomized trial model is not new. In reality, the term pragmatic can be used to express two different concepts. One is the practical trial, comparable to the best historical trials with linear, simple protocols, a defined and clinically important goal, non-redundant datasets, careful protocol management, with a lot of attention to clinical endpoints and follow-up times. Other are the ‘remote or siteless or patient-centred or virtual or digital’ trials, all called pragmatic, because they all share a new methodological characteristic, the entirely digital management of the study. This fundamental management aspect of the trials would have been reached anyway, in harmony with the current very rapid penetration of digital technology in daily life, but it is certain that the connection problems created by the pandemic, including smart work and a close hospitalization accelerated the process. Moreover, virtuality is
considered the maximum of simplification (hence the ‘pragmatic’) and therefore of the optimization of the design, because it implies a substantial (or total) mutual physical disengagement between doctor and patient, with which the connection is based on direct remote IT interactions and on the periodic analysis of IT healthcare pathways—Electronic Health Recordings (EHRs), including each clinical event regardless of enrollment in the study, therefore also the clinical endpoints expected in the trials.

The problem is that the essential operational condition is the existence and completeness of an individual structured electronic medical record, the EHR (or the Electronic Health Record 2–[FSE2] when it becomes operational)—which collects the entire health life of each enlisted subject. This, in turn, presupposes universal digitization in the countries where the study is conducted, given that the record must be fed by any healthcare facility that comes into contact with the subject. It is clear that so far we are not talking about Italy, but about some countries of central and northern Europe, and North America. China is carrying out a forced digitalization of health care, at least in some parts of the country.

In practice, patient enrollment begins with an identification of eligible subjects (very wide inclusion criteria and minimal exclusion criteria) by computer-scrolling a large number of EHRs (from half a million to one million in current studies), to identify a few thousand potential patients. They will be invited to participate in the study, presented with a brief description. Anyone declaring themselves potentially in favor will receive further information and an informed consent form, which they will send back signed to the data collection centre. Once the set of available data has been re-checked, the consenting patient can be enrolled. He will then receive the operational details, and the object of interest for the study, mostly drugs. The visits, if there will be, will be remotely. The collection of physical data, if deemed necessary, will be carried out with appropriate telemetry methods. It must be said that currently many of these can be obtained remotely and transferred, and obviously these technological products will multiply rapidly, but there are currently several obvious obstacles to the optimal collection of data, in particular technological, at home.

Although this ‘pragmatization’ of clinical research has been accelerated by recent events, the process has been going on for about two decades, at least in the USA, where the reference institutions for clinical research had been consensually active for some time. A first formal document was published by The National Academies Press in 2003, a Letter Report titled ‘Key Capabilities of an Electronic Health Record System’, followed by a further article titled ‘Clinical Trials Transformation Initiative’ shared by the FDA, NIH and Duke University, published in 2010. In 2012, after a long and demanding preparation reported in a published text, the NIH and the Duke University launched and simultaneously managed 12 pragmatic trials focused on the most frequent pathology areas. The initiative was called ‘Collaborative’. Such a preliminary experience ended with a workshop conducted in 2018 whose final consideration was very positive for the systematic implementa- tion of pragmatism in trials. In 2016, the FDA took a stand with a document entitled ‘FDA Advancing Medical Innovation’ which confirmed the necessary willingness of the regulator to favourably consider the new methodological approach of the trials. Finally in 2021, therefore in the midst of the pandemic, the US National Academy of Medicine (NAM) 50 (fiftieth anniversary of the Academy) with a document with the explicit title: Embedded Pragmatic Clinical Trials (ePCT) highlight- ing the limits of both conventional randomized trials and observational studies and confirming the priority of randomized pragmatic trials for the clinical study of therapeutic measures.

Again, a very recent article reports a critical review by the FDA on the concepts of real-world data also in reference to their use as real-world evidence for regulatory purposes, with a surprising re-evaluation of observational research and relatively infrequent methods of randomization in relation to the conventional randomization of patients presented as the least suitable for real-world studies.

In addition to institutional issues, there are already articles that discuss the state of the art of the virtual methodology of trials and others that acknowledge its relevance in the current scientific context, finally there are those who deeply analyze concepts and implications of ‘pragmatic approach beyond technicalities. In reality, few clinical trials are classifiable as exploratory or pragmatic. Regardless of the organizational management, most of the studies can be classified at an intermediate point on the continuum between the two prototypes. The problem was therefore raised of measuring the degree of pragmatism of a trial. To do this, there are numerous ways that use numbers of classification domains varying from 2 to 9. Table 3 reports the criteria proposed in a detailed classification, called PRECIS2, which is the most used. In the USA, the pragmatism has been and is intensely advocated as a revolutionary novelty. New it really isn’t. In 1967, about 60 years ago, Schwarz and Lelouch discussed the pragmatic and explanatory approaches of nascent trials with arguments almost identical to those used today by the NAM in the document mentioned above which basically consists in the belief that many trials do not inform clinical practice because they are designed to evaluate the pathophysiological mechanisms of efficacy. Other considerations, such as those reported at the beginning of this article regarding conventional trials are not external in the present position but a reduced US representation in international trials is also relevant, and therefore a questionable generalizability of the results in the USA (which worries the FDA). However, this can be associated with a drop of confidence in the trials’ results got in the USA if the local real-world conditions may be prominent in the trials’ results, as seems to occur with the pragmatic trials if, for instance, the enrollment criteria adopted in the CONGESTION (?) HF trial, similar
to the classical ‘all comers’ trial, would be generally adopted.9

The new Fascicolo Sanitario Elettronico 2 (our Electronic Health Record 2) is (almost) at home! Much of Europe in digital science has been there for some time, without the clamor of revolutionaries or innovators. Especially in terms of registers, most frequently or conceptual path followed in the USA to reset their Health System about 15 years ago. The focus was on considering health information as a structural element of health and technological tests with their respective reports, emergency room reports, documentation of each hospitalization, prescribed therapies, out-of-hospital therapeutic paths, co-morbidities, vaccinations, etc., for life, and pending to include genotype, microbiome.

Some operational aspects are: (i) the Regions will have to draw up the regional files within three months of the approval of the law (therefore by June 2022) based on specific guidelines. Failing this, the national model will be applied (ii) the inclusion in the ESF2 of the data of all health services is mandatory within five days of delivery, (iii) the rules apply to all health institutions: public, accredited private and authorized private, (iv) according to the PNRR (from which the funds come) the whole of the new Health System, which will host the ESF2, must be fully operational by 2026. (v) AGENAS is responsible for managing the IT structure of the entire ECOsystem. (vi) total funding envisaged: approximately 20 billion (40% in the South), €628 million for the EDF2. Overall, the ESF2 will provide in real time the detailed epidemiology (therefore also regional) of the country, the only tool that can really allow the intelligent (because informed) political government of regional and national health. The data, if complete and interoperable, with the support of artificial intelligence as digital, will be excellent material for scientific health research, not just epidemiological ones.

What has been developed in the PNRR is not just a health management tool but a new Health System based on some clear principles that somehow re-propose a conceptual path followed in the USA to reset their Health System about 15 years ago. The focus was on considering health information as a structural element of health and therefore, technically, of Health. The modernization of the ESF2 starts from here. The final track in the USA was the Health Information Technology for Economic and Clinical Health Act which linked the health aspects to the economic aspects with a consequent almost universal adoption of certified EHRs.

For the type of data collected and for the necessary continuity of the FES2 over the course of its lifetime, the renewal of territorial assistance with ‘proximity care networks’ is also relevant (PNRR, DM71, law no. 234/2021). Three areas are focused: (i) telemedicine, (ii) integrated home care and (iii) the management of the chronic patient (PDTA). The PON GOV Chronicity project envisaged a study with a selection of innovative regional experiences in the areas of interest.

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An alert

Given the heterogeneity and dispersion of our Health System, it is easy to predict that there will be an infinite number of problems to be addressed for a homogeneous, rational, and usable implementation of the new Health System, but this is a great opportunity! Some key problems concern the fundamental FAIR characteristics of the data collected: quality is the first, often not even mentioned because it is obvious, but vital, dependent on the quality of the systematic control of the incoming data flow. Others are canonical, but equally essential: accessibility, traceability, reusability, data interconnectivity and finally, ‘sine qua non’, interoperability. In a word, the usability of the data for the purposes for which they were stored. Over 10 years ago, strong federal pressure was exerted in the USA on the nationwide health-care digitalization, costing many tens of billions of dollars. To limit the corporate side of the problems, no restrictions were placed on the individual choice of software by healthcare facilities. Thousands of companies rushed into this sudden dollar shower. An inextricable Babel emerged, which in part still lasts today. The latest date for standardization by health facilities—under penalty of very high penalties—was 2018. A few months ago the very latest date was brought to the end of 2023. In practice, it took about 15 years for an interoperable implementation in the country. The German ministry and the French ministry of health have made available an extensive list of telemedicine software (187 in France). The heterogeneity of EHR software, which undermines the interoperability of the system, is the biggest and most difficult obstacle to eradicate once consolidated. It is necessary to prevent it. With reference to the specific problem of EHR interoperability, it is reported in the literature that in 2021 there were still 17 EHR software networks in the UK and 18 in the USA. The still unsatisfactory arrival points of a 10-year struggle. The greatest risk for us will be regional inhomogeneity. We could not afford a 10-year reorganization.

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