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Adapting to survive

Are ‘classic’ clinical trials at risk for extinction in the post-COVID era?

In current times, all of us are ‘forced to adapt’ to the new, unexpected environment created by the Coronavirus pandemic. Indeed, the ability to adapt to a changing environment is the key to successful evolution. People, healthcare systems, hospitals, economy, governments, etc., all have to adapt! Clinical science, which is typically linked to rigid schemes and protocols, is not exempt and large classic clinical trials are embracing the so-called ‘adaptive designs’.

Why the switch to adaptive trials?

It is a necessity. In the last two decades, the world has experienced six large viral epidemics: influenza H1V1, HIV-AIDS, Ebola, SARS-1, METS, and the present COVID-19 (or SARS-2). The last three belong to the same family: the Corona viruses. All the previous epidemics ceased, more or less, spontaneously. Actually, they became and still remain endemic. The scientific world was not particularly upset, mainly because these epidemics remained confined to a few areas with local specificities. Several new drugs were tested but at the end, no cure was found nor were vaccines produced.

To the contrary, the reaction of the Scientific World to the present pandemic has been and is strong and planetary. More than 4000 studies addressing various aspects of COVID-19 are registered on ClinicalTrials.gov, including more than 600 interventional studies. Among them 29% were not randomized and 64% were single-centre studies. Chloroquines were the most commonly tested intervention, 23% of randomized trials, a minority on prevention.¹ An excess of 7000 papers on COVID-19 are reported in PubMed. Scientific journals are literally flooded by these articles to the point that having an article sent to the referees is already a great success, the majority being refused right away. Enormous efforts and money are ongoing towards the search for vaccines, with governments and companies fighting to be the first. At least 10-vaccine candidates have entered the human testing phase, with more than 80 others at preclinical stages.

Let us hope that effective and safe vaccines will arrive one day. But, today, we urgently need drugs not only for curing sick people, but also for preventing the disease in subjects infected and still asymptomatic and in those who have recovered from the disease but are at potential risk for recurrence.



Figure 1 The ability to adapt to a changing environment is the secret of animal evolution. Even the 'machine' of clinical trials must be able to find flexibility and ability to change in the face of acute and dramatic changes in clinical reality.

Table 1 General characteristics of traditional and platform trials^a (From Berry SM et al. JAMA 2015;313:1619-1620)⁷

Characteristic	Traditional trial	Platform trial
Scope	Efficacy of a single agent in a homogenous population	Evaluating 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 treatments requiring evaluation
No. of treatments 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 federal or industrial sponsor	The trial infrastructure may be supported by multiple federal or industrial sponsors or a combination

^aPlatform trials and similar trials may also be called basket, bucket, umbrella, or standing trials.

The early progresses

Randomized clinical trials (RCTs) have already produced some results: hydroxychloroquine enrolment was stopped due to lack of benefit in hospitalized patients in the two largest ongoing RCTs: RECOVERY (University of Oxford Clinical Trials.gov: NCT04381936) and SOLIDARITY (WHO ClinicalTrials.gov NCT04315948) that includes the DISCOVERY trial (French Government ClinicalTrials.gov NCT04315948). Also, in the same trials the Lopinavir/Ritonavir and

Lopinavir/Ritonavir + Interferon β -1 have been discontinued for lack of benefit. On a happier note, the ACCT trial (NIH ClinicalTrials.gov NCT04292730) showed some benefits for Remdesivir in shortening the time of recovery in hospitalized patients with modest pulmonary disease² and the low-dose Dexamethasone arm of the RECOVERY trial has shown efficacy in severely ill patients. The 28-day mortality was 29% for treated patients as compared with 41% in the usual care group.³

For all the above-mentioned trials and for at least 10 more still ongoing, the investigators selected the same 'unusual' trial design: the so-called adaptive model.

An adaptive trial? What is it?

An 'adaptive' trial is defined as 'a design that allows for prospectively planned modifications to one or more aspects of the trial based on accumulating data from subjects in the trial' (FDA).⁴ Several papers carefully describe the principles and applications.^{5–7} In principle, the adaptive trial designs are based on a flexible methodology aimed at 'adapting' the trial design and performance to specific dynamic characteristics of the study, emerging from the investigator observations and from interim analyses (blinded or not-blinded), to allow to achieve the expected answers quickly and (hopefully) precisely. For instance, a trial arm may be stopped for efficacy, futility, harm, but also for evidence of benefit or damage emerging from another well-designed contemporary trial. Hence, the trial can be concluded when an answer is obtained instead of when a prefixed sample size is achieved. The central characteristics of the trial can also be changed during its course, inclusion and exclusion criteria can be modified, the criteria for randomization, and even the endpoints can be changed, switching from non-inferiority to superiority and adapting the alpha spending functions. Often, adaptive trials test multiple treatments and treatment groups can be adapted: participants to a group which is promising can be enlarged or, vice versa, reduced or just limited to a specific phenotype. New arms can also be activated during the course of the main trials and so on.

The Devil is in the details

All this seems (too) good, logical, and practical but . . . the integrity of the trial must be preserved. The modifications need to be: (i) **prospectively planned**, namely written in the protocol prepared before the trial onset; (ii) **based on accumulating data from subjects in the trial**, namely from the interim analyses.⁴ This means a careful and often difficult planning with the skill to anticipate all the possibilities in advance. According to different degrees of freedom on potential design, trials are categorized as exploratory or confirmatory.

The voice of the authorities

Both the European Medicine Agency (EMA)⁸ and the US Federal Drug Administration (FDA)⁴ have released *ad hoc* documents for the adaptive trial methods, including the important possibility of 'conditional approval'. Regulators seem to encourage the adaptive options. For instance, the FDA underlines the following advantages:

1. adjusting the design according to information not available at the beginning of the trial (this is particularly appropriate in new conditions such as the COVID-19 breakout);
2. statistical efficiency can be improved in the case of smaller than expected sample size or shorter duration of the trial (useful in the context of the variable course of an epidemic);
3. favouring ethical aspects, including the possibility to stop a futile trial earlier, or to focus on one promising arm.

Finally, the FDA states the four key principles to be satisfied by an adaptive design:

1. 'the chance of erroneous conclusions should be adequately controlled;
2. the estimation of treatment effects should be sufficiently reliable;
3. details of the design should be completely pre-specified; and
4. trial integrity should be appropriately maintained'.

The document also anticipates the numerous traps, mostly statistical, that the adaptation design may cause with appropriate suggestions on how to avoid or solve these.⁴

The EMA caught the essence of the adaptive designs underlying their flexibility during the course of the trial, with the efforts to make studies more efficient (e.g. shorter duration, fewer patients), and more informative by adapting to the questions that the interim analyses can raise.⁹

Our considerations

These are the reasons why, in the present outbreak, scientists and regulators have decided to implement the adaptive design for clinical research. We believe it is the right decision considering the pressing urgency and the uncertainty on what to do or not to do, providing that the necessary rigor and integrity is preserved, as the results of the current trials will decide the life or death of hundreds of thousands of people. Outside the COVID-19 outbreak, a new era for the flexible trials design may arise, also in cardiology. Meantime, an unprecedented spread of different scientific methodological approaches to the same target—the COVID-19 infection—allows a unique experimental exercise worldwide. This leads to a great increase of knowledge, experience and ultimately will make the world ready for future viral epidemics.

The 'Ebola story' is grounds for some optimism. During the 2014–2016 Ebola outbreak in West Africa, many small studies were launched, in the end all inconclusive. The virus remained endemic with periodic smaller outbreaks until 2018–2020 when in the Democratic Republic of the Congo two effective therapies were finally identified.⁹ Let us wait and hope for the best.

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References are available as [supplementary material](#) at *European Heart Journal* online.