Since the CCIF had been continuously held for 23 years, for many scientists the conference is a chance to share research, learn innovative skills, and meet future collaborators. However, feedback shows that the virtual online CCIF gave most of the participants equal or even better experiences compared with previous in-person meetings, because of the following features and advantages. (i) A minimum of 60% reduction in costs was achieved. (ii) The online conference was able to improve accessibility, cut down on researchers' carbon footprints, and reach a wider audience than a conventional meeting could. Furthermore, all the scientific contents are archived and can be replayed in the future, which is much better for continuous education purposes. (iii) The past conferences used to be held in big cities. Physicians from rural, low-income districts would previously not have had the time or resources to attend in person to learn the standard techniques and novel concepts presented. Because these rural doctors are better able to attend online, this should help narrow the gap between low-income districts and improve the imbalance of healthcare delivery. (iv) These logistic advantages also helped presenters and panellists. In previous conferences, many of the presenters might have had to cancel, but for CCIF 2020 the cancellation rate was <2%.

Since this was the first attempt at an entirely online meeting on such a large scale, the approach had several teething problems that had to be addressed. Round-table discussions were more difficult to coordinate online, and more work is needed both in technology and in organization to make this a smoother experience.

As stated in the opening speech of CCIF, 'Because we have no other option, we have to experiment, to learn and to transform'. In conclusion, the 23rd CCIF has demonstrated the revolutionary benefits achievable by moving large scientific meetings online.

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Key words to be adopted for COVID-19 research

A return to simple, large, randomized trials

In 1984

An outstanding article was published by Salim Yusuf, one of the 'gurus' of clinical research.[1] The article set out the rules for cardiovascular research worldwide. A few years later, the trials for the treatment of acute myocardial infarction (MI) modified the treatment for this number one killer[2,3] and were followed by studies that contributed to the great success of cardiology.

Today

And this is a 'gift' from COVID-19, the lessons learnt seem to have been lost. A multitude of small, often uncontrolled clinical trials have started or are on the way, based on enthusiasm, but we risk wasting human and economic resources.

Why such a pessimistic view?

Because doctors are not magicians! Any proposed treatments for COVID-19 cannot provide miraculous results, but rather small to moderate favourable effects. Hopefully small pilot/exploratory studies can open the door to new avenues, but still, even today, the priority has to be to plan and conduct large, simple, randomized trials.

Why large?

With the little knowledge we have about this pandemic, we can expect only moderate treatment effects. To reliably demonstrate a moderate benefit, we need several thousands of patients. Let us take as an example MI. At the beginning of the 1980s, the in-hospital mortality rate was ~12–13%, and the effective treatments (thrombolysis and aspirin) reduced it by ~20%: from ~13% to 10%. Large trials with 12 000[2] and 17 000[3] patients were necessary to provide reliable results which were useful to change, in a brief period of time, clinical practices all over the world. In absolute terms, a moderate relative reduction of mortality corresponds to a huge number of lives saved globally.

The context of COVID-19 is similar: a small relative moderate reduction of deaths will produce an enormous impact on the absolute number of people who can survive after a hospitalization for the COVID-19 infection. In addition, patients affected by COVID-19 are

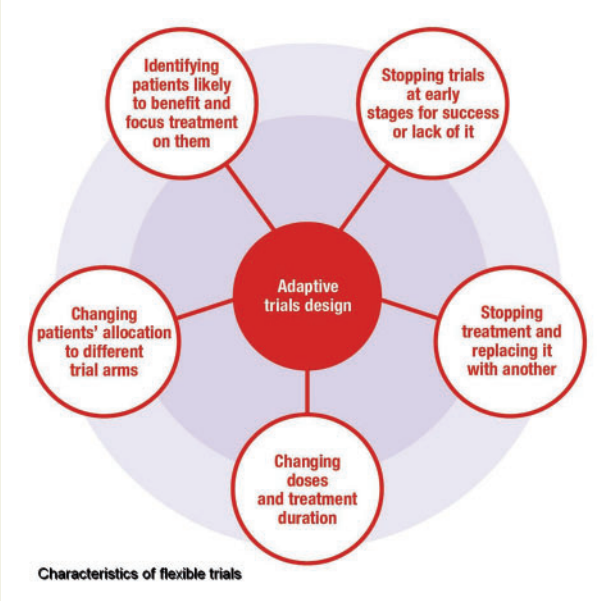

Figure 1

not all the same. They have different degrees of severity due to virulence of the infection and underlying comorbidities.

Large numbers of patients are needed to identify subgroups (age, sex, comorbidities, severity of the disease, etc.) who will benefit to some extent and can enjoy a greater benefit or those for whom the safety issues may counterbalance a possible favourable effect. This will help us to select the most appropriate patients for a specific treatment.

Furthermore, COVID-19 is a global problem. Different healthcare systems and socio-economic conditions have an impact on the outcomes of affected patients. These differences can only be revealed by a large, global trial.

Why simple?

Every country is currently practising a form of emergency, disaster medicine. Hospitals have changed their organization and structure. Under these circumstances, it is not possible to follow the interpretation of GCP-ICH rules. We need to maintain the basic principles of these rules, but to put aside obsessive details, to safeguard the rights and safety of patients and the scientific integrity of the study. Simplicity, today, is the keyword.

Routine clinical activities are a priority; the participation in a streamlined trial should consist of no more than a brief web connection to randomize the patient and to receive the arm of treatment. Forget paper documentation with endless forms to complete; just web inclusion of a small number of variables, to describe demographics, clinical characteristics, and severity of the report of serious unexpected adverse reactions, and reasons for treatment discontinuation should be enough for safety.

The primary and secondary endpoints need to be easy to detect and indisputable: hospital mortality, length of stay, and invasive ventilation, all via the internet, at hospital discharge. In practice, no more than 10–15 min of activity per patient would be needed to adequately complete the study.

Why randomized?

Randomization is necessary to avoid bias in the interpretation of the results and not to fuel the fire of overenthusiastic expectations. In a situation of ignorance in politicians and governments, at the very least the medical community needs to be trusted. A recent article published in the *New England Journal of Medicine* comprehensively discusses why it is essential to trust randomization.[4]

What can we do now?

Please consider being part of two **large, simple, and randomized trials**: the RECOVERY trial (www.recoverytrial.net) designed by the University of Oxford which has recently started recruiting patients, and the SOLIDARITY trial designed and conducted by the WHO (https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—18-march-2020) which will begin recruiting very soon. Other studies will follow.

These trials will test the most promising treatment strategies with an undisputable primary endpoint: all-cause in-hospital mortality. Antiviral agents, such as remdesivir, hydroxychloroquine (or chloroquine, depending on local availability), lopinavir (co-formulated with ritonavir, to slow hepatic degradation), and interferon (β1b) will be evaluated. These two studies are examples of **adaptive trials**.

The situation we are facing is extremely challenging and clinical research should adapt to this.

Nobody is sure about testing the right drug (no pre-clinical data). Thus, it is reasonable to test several dugs in parallel. Nobody is sure about doses and duration of treatments. It is, then, logical to have more than one arm testing different doses and duration. Drugs are tested against an unknown condition: COVID-19. Interim analysis should be performed to capture early positive or negative signs of benefit.

The pre-planned actions for a flexible design are listed in *Figure 1*.

In conclusion

Let us be flexible and able to adapt. Large, simple, randomized . . . and, most importantly, work together! **It is the only way to prevail, and we will.**

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References are available as supplementary material at *European Heart Journal* online.