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

Participants' informed consent in adaptive, platform drug trials in hospitalized COVID-19 patients: Not all approaches are ethically acceptable

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One of the most exciting bits of news that the COVID-19 pandemic has provided in the clinical research arena is demonstrating that adaptive, platform randomized controlled trials (ad-RCTs) provided useful responses about clinical efficacy and safety of medicines in reasonable time frames. Among others, four of these ad-RCTs (Discovery [1], RECOVERY [2], REMAP-CAP [3], Solidarity [4]), have shown that some of the trial antiviral therapies were efficacious in the treatment of hospitalized COVID-19 patients compared to control groups receiving the standard of care. The robustness of the design and the appropriate conduct of these ad-RCTs have made them examples of the type of RCT that should be carried out in future pandemics and other circumstances when rapid therapeutic responses are needed to address emerging clinical situations.

These four ad-RCTs share many characteristics, such as being sponsored by non-commercial organizations; making trial protocols public [5–8]; being simple, open label, large RCTs that mainly assessed repurposed medications through the recruitment of thousands of participants; and which published results in top-ranking journals that have had a critical influence on the evolving standard of care [9].

A fifth ad-RCT, the I-SPY COVID Trial [10], is built on the experience investigators gained in a previous ad-RCT on breast cancer. This trial is a unique collaborative effort by a consortium that included the US FDA, industry, patient advocates, philanthropic sponsors, and clinicians from major US medical research centers [11]. Unlike the other ad-RCTs mentioned above, which are phase 3 RCTs, it is a phase 2 trial for rapidly screening and triaging potential treatments [10]. The I-SPY COVID Trial, which started in July 2020, evaluates in parallel up to four (repurposed and novel) medications vs a control (remdesivir; dexamethasone was added later) on top of the standard care for severe COVID-19 patients. Using a Bayesian approach, assessing 40-125 participants per group allowed dropping medications due to futility or 'graduate' for superiority [12]. Of the over 70 individual agents reviewed, 12 were included in 11 trial arms (one arm was a combination of two drugs); 8 arms have been already completed [12].

Obtaining participants' informed consent is one of the basic safeguards for ensuring ethically conducted clinical research. Investigators must provide potential participants all reasonable relevant trial information so that they can make an informed decision. How investigators seek participants' informed consent should be consistent with international ethical standards. First, informed consent must be obtained from patients with capacity. If a patient is incapable of consenting (e.g., intubated patient), the investigator must seek informed consent from their legal representative [13,14]. During the pandemic, at the trial design stage, investigators of the four aforementioned ad-RCTs (Table 1)

Abbreviations: ad-RCT, adaptive, platform randomized controlled trial; FDA, Food and Drug Administration; RCT, randomized controlled trial.

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decided that deferred consent was an acceptable approach as they realized that many potential trial participants would be incapable of providing consent and having access to the patient's legal representative could be extremely difficult to obtain. Their decisions were backed by the research ethics committees involved in the review and approval of the ad-RCTs' protocols. Patients unable to consent were included in the trial and informed consent obtained once they were able to provide it (or when the legally authorized representative became available), rendering the consent deferred [13,14]. However, deferred consent must fulfil several conditions to be ethically acceptable [15]. Second, trial investigators should seek the informed consent of potential participants before randomization, which ensures that all participants receive the same information on the trial procedures and available treatments in all study arms. This is applicable to any RCT, but it is even more relevant when it is likely that the legal representative of many participants will be involved. The participant's legal representative should decide considering to what extent study participation promotes the individual's clinical interests [14], and to this end should know all the therapies under assessment.

The I-SPY COVID Trial used a completely different informed consent approach: randomization precedes obtaining participants' informed consent. Patients requiring high-flow oxygen are eligible for the trial and are randomized to the control arm or to any of the experimental medications. Investigators seek participants' informed consent *only after* they are assigned to a specific medication. Participants were informed about the assigned experimental medication but not about the other experimental agents being assessed as well as the existence of a control group [12]. Is the decision of the I-SPY COVID Trial investigators to utilize a post-randomization consent approach ethical?

Modifications of informed consent are generally recognized as ethically and legally acceptable (in some jurisdictions) if, at least, three requirements are met–The research has important social value, it poses no more than minimal risks to participants, and it would not be feasible or practicable to carry out the research without the modification [13,16,17]. The I-SPY COVID Trial fulfils the first requirement, since any well-designed trial aiming to assess the efficacy of medications in the treatment of hospitalized COVID-19 patients has important social value. It is debatable whether it fulfils the second, but it does not fulfil the last.

It can be argued that when dealing with hospitalized COVID-19 patients, even if being treated with remdesivir and dexamethasone, trial participants are exposed to more risks than 'may be subsumed under minimal risk' [18]. Conversely, others might argue that for participants of the experimental groups, a post-randomization consent approach could be acceptable if participants were exposed to repurposed medications —with a well-known benefit/risk ratio— but not with novel agents. Nevertheless, as mentioned, other ad-RCTs involving hospitalized COVID-19 patients have been conducted without modification of the consent process.

The method of randomizing participants before acquiring consent was first proposed by Zelen in 1979 [19]. Only participants randomized to the experimental arms should consent and receive information regarding only the assigned treatment. Those in the control group would not be informed that they were participating in a trial. Zelen thought that this design would likely enhance recruitment. Furthermore, since the control group patients would not be aware of the presence of alternative treatments, their expectations would not be impacted. Hence, they are less likely to suffer from 'resentful demoralization' which can bias the trial's results by, for example, increasing the likelihood of drop-outs [20]. Zelen's design has been used mainly to assess interventions or specific strategies applied to the real-world, such as outreach, engagement, and health promotion interventions [21]. It is rarely employed in clinical research and is exceptionally used in drug trials [20]. It is also considered to be poorly suited to address explanatory trials [21], such as the I-SPY COVID Trial.

'Just-in-time consent' [22] and 'Trials within cohorts' [23] (or 'cohort multiple RCT') are recent updates of Zelen's design. In these two methods, potential participants are first included in observational cohorts. Later, members of these cohorts are randomized to receive an experimental intervention or standard of care. The informed consent discussion is split in two stages. First, participants consent to be included in the cohort, and are informed of their potential inclusion in a clinical trial. Second, participants are then randomized–Those assigned to the experimental group are asked for their consent. Those assigned to the control group provide standard clinical consent [22] or can be considered to have already given their consent to the trial at the time they were included in the cohort, so they are not asked for a second consent [23]. In both situations, participants in the control group are not provided with any information about the experimental interventions [22,23]. With both updated designs, 'resentful demoralization' is prevented in the control group. Control group participants in studies that employ 'Just-in-time consent' and 'Trials within cohorts' designs would therefore not know that their assignment was made by a random process [22,23].

Consent to RCTs should fulfil three ethical features [24]: participants must agree to contribute to the trial, this must be known at the time they are recruited, and they must know that they have participated in it. 'Just-in-time consent' and 'Trials within cohorts' designs do not fulfil these three features for all participants.

I-SPY COVID Trial investigators did not seek (and are not seeking) participants' informed consent before randomization. However, data from other RCTs (Table 2) clearly suggest that I-SPY COVID Trial could have been conducted with a pre-randomization informed consent approach. Hence, unfeasibility or impracticality cannot be alleged. Claiming that post-randomization consent approach is more patient-centered, as it reduces burden on participants and surrogates [12], is not an ethically valid reason to omit important information to patients

Table 1
Main features of participants' informed consent process in four large adaptive, platform, randomized controlled trials assessing medications to treat hospitalized COVID-19 patients, and the informed consent text included in published articles.

Trial name (Sponsor)	Participants' informed consent process		Informed consent text included in articles	Countries where the trial was conducted
	When it is obtained	Who provides it	*Text*	
DISCOVERY (INSERM, France)	Before enrollment	Patient, legal guardian or relative [5]	"Written, informed consent was obtained from all participants or from their legal representative if they were unable to provide consent." [1]	Austria, Belgium, France, Luxembourg, Portugal
RECOVERY (University of Oxford, UK)	Before enrollment	Patient, relative acting as patient's legally representative or independent doctor. Deferred consent–Accepted [6].	"Written informed consent was obtained from all the patients or from a legal representative if they were unable to provide consent." [2]	UK
REMAP-CAP (UMC Utrecht, The Netherlands)	Before enrollment	Patient, legal representative or waiver-of-consent (this latter for interventions being part of standard of care). Deferred consent–Accepted [7].	"Written or verbal informed consent, in accordance with local legislation, was obtained for all patients or from their surrogates." [3]	Australia, Canada, France, Ireland, the Netherlands, New Zealand, UK, USA.
SOLIDARITY (World Health Organization)	Before enrollment	Patient or representative. Deferred consent–Accepted [8].	"Written informed consent was provided by patients, or if they were unable to do so, by their legal representatives." [4]	30 countries, in four continents

Table 2
Main features of four adaptive platform randomized controlled trials assessing medications to treat hospitalized COVID-19 patients and that of I-SPY COVID trial.

Trial name (ID)	Hospitalized patients needing supplemental oxygen (≥WHO COVID level 5)	Number of treatment groups [a]	Number of randomized participants	Number of sites	Recruitment period (number of months)	Recruitment rate (participants /month) [b]
DISCOVERY [1] [c] (EU 2020-000936-23)	99%	5	857	48	10	1.8
RECOVERY [2] [c] (ISRCTN50189673)	76%	2	6,425 (4,890) [d]	176	3	12.2 (9.3) [e]
REMAP-CAP [3] [c,f] (NCT02735707)	99.7%	3	403	121	3	1.1
SOLIDARITY [4] (ISRCTN83971151)	71%	5	11,330 (8,062) [d]	405	3-6 [f]	9.3-4.7 (6.6-3.3) [e]
I-SPY COVID [10] (NCT04488081)	100%	11[g]	2,100	30	15[h]	4.7

[a] Including the control (standard of care) group.
[b] Considering that all sites were active during the whole time.
[c] The first report of a series of articles.
[d] In brackets–The number of participants needing supplemental oxygen.
[e] In brackets–The recruitment rate of participants needing supplemental oxygen.
[f] REMAP-CAP trial was designed before COVID-19 pandemic to determine best treatment strategies for patients admitted to an intensive care unit with severe community-acquired pneumonia. In this article, 71.6% of recruited patients had confirmed SARS-CoV-2 infection.
[g] Each of the experimental medications was assessed between 3 and 6 months. Currently there are only 3 active drug arms.
[h] The trial started in July 2020 and the I-SPY Consortium [10] article was published in January 2022. We have considered that the 2,100 participants were recruited in 15 months. No article on any assessed drug has yet been published in a peer-reviewed journal.

(or their legal representatives) to decide whether to participate in an ad-RCT. A global response for the next pandemic requires, among others, uniform ethical approaches to on how, when and to what participants are consenting when they participate in ad-RCTs.

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Rafael Dal-Ré: Conceptualization, Writing – original draft, Writing – review & editing. **Arthur L Caplan:** Writing – review & editing. **Teck Chuan Voo:** Writing – review & editing.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

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