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Study Design

The Anti-Coronavirus Therapies (ACT) Trials: Design, Baseline Characteristics, and Challenges

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ABSTRACT

Background: Effective treatments for COVID-19 are urgently needed, but conducting randomized trials during the pandemic has been challenging.

RÉSUMÉ

Contexte : Il est urgent de mettre au point des traitements efficaces contre la COVID-19, mais il n'est pas facile de réaliser des essais à répartition aléatoire dans un contexte pandémique.

Patients with COVID-19 most commonly experience mild symptoms. Increasing severity of disease is accompanied by a hypercoagulable state and dysregulated immune response, and can result in respiratory failure, multiorgan dysfunction, and death.[1,2] Initial efforts to identify effective therapies for COVID-19 focused on repurposing existing drugs to target the virus, hypercoagulability, or inflammation, but most trials have been inadequately powered, and few treatments have

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Ethics Statement: The research reported has adhered to the relevant ethical guidelines.

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See page 576 for disclosure information.

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Methods: The Anti-Coronavirus Therapy (ACT) trials are parallel factorial international trials that aimed to enroll 3500 outpatients and 2500 inpatients with symptomatic COVID-19. The outpatient trial is evaluating colchicine vs usual care, and aspirin vs usual care. The primary outcome for the colchicine randomization is hospitalization or death, and for the aspirin randomization, it is major thrombosis, hospitalization, or death. The inpatient trial is evaluating colchicine vs usual care, and the combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily vs usual care. The primary outcome for the colchicine randomization is need for high-flow oxygen, need for mechanical ventilation, or death, and for the rivaroxaban plus aspirin randomization, it is major thrombotic events, need for high-flow oxygen, need for mechanical ventilation, or death.

Results: At the completion of enrollment on February 10, 2022, the outpatient trial had enrolled 3917 patients, and the inpatient trial had enrolled 2611 patients. Challenges encountered included lack of preliminary data about the interventions under evaluation, uncertainties related to the expected event rates, delays in regulatory and ethics approvals, and in obtaining study interventions, as well as the changing pattern of the COVID-19 pandemic.

Conclusions: The ACT trials will determine the efficacy of anti-inflammatory therapy with colchicine, and antithrombotic therapy with aspirin given alone or in combination with rivaroxaban, across the spectrum of mild, moderate, and severe COVID-19. Lessons learned from the conduct of these trials will inform planning of future trials.

Méthodologie : Les essais internationaux factoriels ACT (*Anti-Coronavirus Therapy*) avaient un objectif d'inscription de 3 500 patients externes et de 2 500 patients hospitalisés présentant une COVID-19 symptomatique. L'essai mené auprès de patients externes visait à évaluer la colchicine par rapport aux soins habituels, et l'aspirine par rapport aux soins habituels. Le paramètre d'évaluation principal au terme de la répartition aléatoire des patients était l'hospitalisation ou le décès dans le groupe traité par la colchicine, et la thrombose majeure, l'hospitalisation ou le décès dans le groupe traité par l'aspirine. L'essai mené auprès de patients hospitalisés visant à évaluer la colchicine par rapport aux soins habituels, et un traitement associant le rivaroxaban à 2,5 mg deux fois par jour et l'aspirine à 100 mg une fois par jour par rapport aux soins habituels. Le paramètre d'évaluation principal au terme de la répartition aléatoire des patients était le recours à l'oxygénothérapie à haut débit ou à la ventilation mécanique ou le décès dans le groupe traité par la colchicine, et la survenue de manifestations thrombotiques majeures, le recours à l'oxygénothérapie à haut débit ou à la ventilation mécanique ou le décès dans le groupe traité par l'association rivaroxaban-aspirine.

Résultats : À la fin de la période d'inscription, le 10 février 2022, 3 917 patients externes et 2 611 patients hospitalisés formaient la population des essais. Certains aspects se sont révélés problématiques, notamment le manque de données préliminaires sur les interventions à évaluer, les incertitudes liées aux taux d'événements prévus, les retards touchant les approbations réglementaires et éthiques et les interventions de recherche, de même que l'évolution de la pandémie de COVID-19.

Conclusions : Les essais ACT détermineront l'efficacité du traitement anti-inflammatoire par la colchicine et du traitement antithrombotique par l'aspirine, administrée seule ou en association avec le rivaroxaban, contre la COVID-19 légère, modérée ou sévère. Les leçons tirées de ces essais orienteront la planification d'essais ultérieurs.

been shown to be effective.[3-5] In combination with non-pharmaceutical methods, vaccines are expected to be the most effective way to reduce the burden of COVID-19,[6] but many countries have only limited access to vaccines, and even where the vaccine is widely available, hesitancy has limited uptake, and breakthrough infections still occur.[7] Continued evaluation of potential therapies for COVID-19 therefore remains important.

Targeting inflammation using glucocorticoids[3] (eg, dexamethasone) or immunomodulators[4,5] (eg, tocilizumab, baricitinib) reduces mortality in hospitalized patients with COVID-19. The advantage of glucocorticoids is that they are inexpensive and widely available, but they have many side effects, including increased susceptibility to life-threatening infections,[8] whereas immunomodulators are unaffordable in many parts of the world. To date, anti-inflammatory therapies have not been shown to be effective in outpatients. Colchicine is a simple, inexpensive anti-inflammatory drug that has been used for more than 40 years at low doses for treatment of gout and familial Mediterranean fever. Colchicine accumulates in neutrophils and monocytes and inhibits the NLR3P inflammasome, which is activated by the SARS-CoV-2 virus.[9] The randomized **Col**chicine **Corona**virus SARS-CoV2 (COLCORONA; n = 4488) trial testing colchicine (0.5 mg twice daily for 3 days, followed by 0.5 mg once daily for 27 days) in outpatients,[10] and the Effects of **Col**chicine on Moderate/High-risk Hospitalized **COVID**-19 Patients (COLCOVID) trial (n = 1279) testing colchicine (loading dose followed by 0.5 mg once daily for up to 14 days) in inpatients,[11] produced promising but not definitive results, whereas the much larger **R**andomised **E**valuation of **COV**ID-19 Th**er**ap**y** (RECOVERY) trial (n = 11,340) did not demonstrate a benefit of colchicine in inpatients.[12] In the RECOVERY trial, patients received a loading dose of colchicine, followed by 0.5 mg twice daily for up to 10 days. In the **A**nti-**C**oronavirus **T**herapy (ACT) outpatient trial, we are evaluating colchicine 0.6 mg twice daily for 3 days, followed by 0.6 mg once daily for an additional 25 days in outpatients, which is similar to doses that were tested in the COLCORONA trial. In the ACT inpatient trial, we are testing colchicine given as a loading dose of 1.2 mg, followed by 0.6 mg 2 hours later, and then 0.6 mg twice daily for 28 days in inpatients (with dose reduction in patients with severe renal impairment), which is a higher dose than that tested in the RECOVERY trial and a longer duration of treatment than that tested in either the RECOVERY or COLCOVID trial.

Hypercoagulability in patients with COVID-19 is accompanied by activation of blood coagulation, including a marked increase in blood levels of D-Dimer.[13] Observational studies report high rates of venous thromboembolism (VTE) in hospitalized patients with COVID-19,[14] whereas postmortem

Table 1. Anti-Coronavirus Therapy (ACT) trials design and planned number of patients per group

ACT outpatient trial			ACT inpatient trial		
	Aspirin (n = 1750)	Control (n = 1750)		Rivaroxaban + aspirin (n = 1250)	Control (n = 1250)
Colchicine (n = 1750)	Colchicine + aspirin (n = 875)	Colchicine + no aspirin control (n = 875)	Colchicine (n = 1250)	Colchicine + rivaroxaban / aspiriny\ (n = 625)	Colchicine + no rivaroxaban/ aspirin control (n = 625)
Control (n = 1750)	Aspirin + no colchicine control (n = 875)	No colchicine controls + no aspirin control (n = 875)	Control (n = 1250)	Rivaroxaban / aspirin + no colchicine control (n = 625)	No rivaroxaban/aspirin control + no colchicine control (n = 625)

studies demonstrate extensive endothelial dysfunction and platelet- and fibrin-rich microvascular thrombosis involving the lungs and other organs.[15] Several randomized trials have evaluated the use of antithrombotic strategies in outpatients and inpatients with COVID-19, to prevent venous and arterial thromboembolic events and mortality, but results have been conflicting, with reductions in VTE accompanied by increases in bleeding and no mortality benefits.[16,17] Aspirin and rivaroxaban are effective antithrombotic drugs when used alone or in combination. Aspirin alone prevents both venous and arterial thromboembolism, including stroke and myocardial infarction.[18] Rivaroxaban 2.5 mg twice daily in combination with aspirin is substantially more effective than aspirin alone for prevention of both arterial events and VTE,[19] and the combination may prove to be an ideal antithrombotic regimen to target microvascular thrombosis. In the ACT trials, we are evaluating aspirin 100 mg once daily in outpatients, and the combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily in inpatients.

Materials and Methods

The ACT program includes outpatient and inpatient randomized trials, testing the effects of anti-inflammatory and antithrombotic therapies in complementary populations. The comparisons between anti-inflammatory therapy and control, and between antithrombotic therapy and control, will be examined separately in each trial, and will also be evaluated in combination across the trials, thereby providing information on the value of these interventions in a broad range of patients with mild, moderate, and severe COVID-19 disease.

ACT outpatient trial

Specific objectives. The primary objective of the anti-inflammatory randomization is to evaluate if colchicine, compared to usual care, prevents hospitalization or death. The primary objective for the antithrombotic randomization is to evaluate if aspirin, compared to usual care, prevents major thrombotic clinical events (myocardial infarction, stroke, acute limb ischemia, pulmonary embolism), hospitalization, or death. The primary objectives will be evaluated during the first 45 days after randomization.

Design. The ACT outpatient trial is a multicentre, international, open-label, parallel group, randomized, controlled trial with a 2 x 2 factorial design of symptomatic patients with COVID-19 (Table 1). The detailed inclusion and exclusion criteria are summarized in Table 2.

Potentially eligible patients are screened by telephone, and those eligible are randomized using a central interactive Web randomization system in a 1:1 ratio to colchicine vs usual care, and in a 1:1 ratio to aspirin vs usual care, stratified by site and using randomly permuted blocks. The dosing regimens of the study interventions are detailed in Table 3.

ACT inpatient trial

Specific objectives. The primary objective of the anti-inflammatory randomization is to evaluate whether colchicine, compared with usual care, prevents the need for high-flow oxygen, the need for mechanical ventilation, or death. The primary objective for the antithrombotic randomization is to evaluate whether the combination of rivaroxaban and aspirin, compared with usual care, prevents major thrombotic clinical events (myocardial infarction, stroke, acute limb ischemia, pulmonary embolism), the need for high-flow oxygen (noninvasive respiratory support that delivers warmed, humidified, oxygen-enriched air to patients, typically at a rate of at least 15 L per minute), mechanical ventilation, or death. The primary objectives will be evaluated during the first 45 days after randomization.

Design. The ACT inpatient trial is a multicentre, international, open-label, parallel group, randomized, controlled trial with a 2 x 2 factorial design in symptomatic inpatients with COVID-19 (Table 1). The detailed inclusion and exclusion criteria are summarized in Table 2.

Potentially eligible patients are screened in person, and those who are eligible are randomized using a central interactive Web randomization system in a 1:1 ratio to colchicine vs control, and a 1:1 ratio to the combination of rivaroxaban and aspirin vs usual care, stratified by site, and using randomly permuted blocks. The dosing regimens of study interventions are detailed in Table 3.

Table 2. Anti-Coronavirus Therapy (ACT) trials eligibility

Criteria	ACT outpatient trial	ACT inpatient trial
Inclusion	Symptomatic and laboratory-confirmed* diagnosis of COVID-19 Age $\geq$ 30 y† Within 7 d (ideally 72 h) of diagnosis or worsening clinically High risk: either age $\geq$ 70 y, or at least one of the following: male; obesity (BMI $\geq$ 30); chronic cardiovascular, respiratory, or renal disease; active cancer; diabetes.\	Symptomatic and laboratory-confirmed* diagnosis of COVID-19 Age $\geq$ 18 y Within 72 h (ideally 24 h) of admission or worsening clinically
Exclusion	Advanced kidney disease (eGFR $<$ 15 mL/min per 1.73 m^2) Advanced liver disease Pregnancy (known or potential) or lactation Colchicine: allergy or planned use (eg, gout); current or planned use of cyclosporine, verapamil, HIV protease inhibitor, azole antifungal, or macrolide antibiotic (except azithromycin) Aspirin: allergy or planned use; high risk of bleeding; current or planned use of other antithrombotic drugs (eg, P2Y12 inhibitors, direct oral anticoagulants, vitamin K antagonists, heparins)	Advanced kidney disease (eGFR $<$ 15 mL/min per 1.73 m^2) Advanced liver disease Pregnancy (known or potential) or lactation Already ventilated for $>$ 72 h Colchicine: allergy or planned use (eg, gout); current or planned use of cyclosporine, verapamil, HIV protease inhibitor, azole antifungal, or macrolide antibiotic (except azithromycin) Rivaroxaban and aspirin: allergy or planned used of rivaroxaban; high risk of bleeding; current or planned use of P2Y12 inhibitors or therapeutic doses of anticoagulants (eg, direct oral anticoagulants, vitamin K antagonists, heparin, low-molecular-weight heparin), current or planned use of strong inhibitors of both cytochrome 3A4 and P-glycoprotein (eg, lopinavir/ritonavir, carbamazepine, ketoconazole)‡

BMI, body mass index; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus.

*Using a locally approved antigen or polymerase chain reaction (PCR) test.

†Originally $\geq$ 18 years; changed to $\geq$ 30 years on July 15, 2021.

‡Note that prophylactic doses of anticoagulants can be used in patients who are randomized to control.

Concomitant therapies

The protocol allows treating physicians to provide usual care according to local practice, except that non-study treatments that could interact with the study drugs should be avoided, unless a clear medical indication for them develops. In such cases, the study treatment would be interrupted. The duration of study treatments is 28 days, but the protocol makes provision to discontinue study treatments earlier when, in the judgment of the clinician, the patient has fully recovered from COVID-19 prior to completing 28 days of treatment.

Outcomes and follow-up

Outcome assessors are not blinded to treatment allocation, and trial outcomes are not adjudicated. Primary, secondary, and other outcomes are summarized in Table 4, and outcome definitions are provided in Supplemental Table S1. Participants will be followed in person or by telephone at day 8, day 45, and 6 months to evaluate adherence and possible use of non-study therapies, and to collect outcomes.

Statistical considerations

The ACT outpatient trial aimed to enroll 3500 patients, which will provide 80% power with a 2-sided alpha of 0.05 to detect a 30% relative risk reduction for each intervention vs control, assuming an overall incidence rate of the primary outcome of 7.5% at 45 days, and allowing for up to 2% loss to follow-up. The ACT inpatient trial aimed to enroll 2500 patients, which will provide at least 80% power with a 2-sided alpha of 0.05 to detect a 20% relative risk reduction for each intervention vs usual care, assuming an overall incidence rate of the primary outcome of 22% at 45 days, and allowing for up to 1% loss to follow-up. Because outpatients with COVID-19 are not as sick as those who are hospitalized, the steering committee felt that, for a new treatment to be adopted, outpatients would need to achieve a larger risk reduction (ie, 30% vs 20% in inpatients).

There will be no adjustment for multiplicity of testing because there is only one primary outcome for each randomization in each trial. Secondary outcomes will be considered as supportive evidence if the results are consistent with the primary outcome, and we will present P values so that the reader will know them. We will not make claims of significance for secondary outcomes unless the results are extreme (eg, $P < 0.001$).

In both trials, the primary hypothesis of efficacy will be tested under the intention-to-treat principle and will include all patients from the time of randomization. Colchicine and antithrombotic therapies have different targets, and there is no biological or pharmacologic rationale for expecting an interaction between these treatments when they are co-administered. However, in each trial separately, a possible interaction between the 2 treatment arms will be assessed by inclusion of an interaction term in the model. Kaplan-Meier curves will be used for a survival analysis, and a Cox proportional hazards model will be used to estimate the hazard ratio and 95% confidence interval. We will perform subgroup analyses to explore whether the treatment effect is modified by age, sex, the laboratory tests used to confirm the diagnosis of COVID-19, vaccination status, timing of enrollment according to the phase of the pandemic, the presence or absence of comorbidities at baseline, disease duration and severity at baseline, and in the inpatient trial, admission to an intensive care unit at randomization and ventilation at randomization.

Analyses will be performed separately for each of the randomizations in the outpatient and inpatient trials, as well as a combined individual patient analysis of the outpatient and inpatient trials for anti-inflammatory and antithrombotic therapy comparisons. The combined analyses will provide $>$ 90% power with a 2-sided alpha of 0.05 to detect a 20%

Table 3. Anti-Coronavirus Therapy (ACT) trials investigational treatment dosing.

Intervention	ACT outpatient trial	ACT inpatient trial
Colchicine*	eGFR ≥ 30: 0.6 mg twice daily for 3 d, then 0.6 mg once daily for 25 d (total: 28 d) eGFR 15 to 29: 0.6 mg once daily for 28 d.	eGFR ≥ 30: two 0.6 mg tablets (1.2 mg) followed by 0.6 mg 2 h later, then 0.6 mg twice daily for 28 d† eGFR 15 to 29: 0.6 mg once daily for 28 d†
Aspirin‡	100 mg once daily for 28 d	100 mg once daily for 28 d
Rivaroxaban	—	2.5 mg twice daily for 28 d

eGFR (estimated glomerular filtration rate) is given in mL/min per 1.73 m^2.

* Depending on availability, 0.5-mg tablets can be used instead of 0.6-mg tablets.

† If eGFR drops to 15 to 29, the dose of colchicine will be reduced to once daily. If eGFR drops to < 15, or creatinine rises by 60% over 24 h or 100% over 48 h, or creatinine rise is accompanied by oliguria or anuria, colchicine and rivaroxaban will be discontinued.

‡ Depending on availability, 75- or 81-mg tablets can be used instead of 100-mg tablets.

relative risk reduction with both anti-inflammatory and antithrombotic treatments.

Translational study

The clinical manifestations of COVID-19 are well described, but we do not know whether changes in blood biomarker levels are related to viral load, predict disease progression and/or end-organ damage, or can be used to evaluate responses to treatment. The specific objectives of the translational substudy are as follows:

1. to assess the impact of experimental therapies (aspirin, rivaroxaban, and colchicine) on viral, inflammatory, coagulation markers (D-dimer, prothrombin time [PT], activated partial thromboplastin time [aPTT], fibrinogen) and markers of end-organ damage and the ability of these biomarkers to predict the likelihood of clinical response (venous and arterial thrombosis, need for intensive care unit admission, or death);
2. to examine the relationships among viral load, inflammation, activation of coagulation, organ dysfunction, and clinical outcome;
3. to examine the prognostic capacity of D-dimer (and other coagulation markers) to identify patients at risk of complications (thrombosis and end-organ damage, such as cardiac and kidney injury) and mortality; and
4. to assess differences in D-dimer levels (and other coagulation markers) in those receiving experimental therapy vs usual care.

The translational substudy is being conducted in Egypt and United Arab Emirates and involves serial collection, from a subset of several hundred outpatients and inpatients, of nasal swabs to measure viral load, and blood samples to measure soluble angiotensin-converting enzyme-2 levels and markers of inflammation, coagulation activation, and end-organ damage (troponin, liver enzymes, and creatinine). These samples are being collected at day 1, day 4, and day 8. Additional details are provided in a separate substudy protocol.

Study management

The ACT trials are overseen by an international steering committee and managed by the Population Health Research Institute. The trials are registered at www.clinicaltrials.gov (NCT04324463). Committee memberships and other trial personnel are listed in Supplemental Appendix S1.

Data and safety monitoring committee

An independent data and safety monitoring committee is monitoring the ACT trials for safety and efficacy. A single formal interim analysis for efficacy and safety will be performed when approximately two-thirds of the target sample size has been enrolled. The interim analyses will be guided by the Haybittle-Peto boundary of 3 standard deviations to indicate benefit. If crossed, it must be confirmed at a subsequent analysis (ie, 2 consecutive crossings) conducted at least 1 month later. The committee will also examine the consistency of efficacy results across both trials and in key subgroups prior to making any recommendations to stop the trial. No modification to the level of significance of final results is needed because of the extreme boundary applied.[20,21]

Challenges of trial conduct

When the ACT trials were first designed, data on event rates were very limited, as were data on potential treatment effects of the planned interventions. Many of the treatments being evaluated were supported by theoretical considerations, and some experimental data, but lacked even preliminary clinical data in patients with COVID-19, and little was known about the expected event rates in this population. To accommodate these uncertainties, the ACT trial protocols made provision for modifications to study design based on emerging data, including dropping treatments and replacing or adding new treatments, as well as changing the sample size.

The ACT trials experienced challenges in startup caused by delays in regulatory and ethics approval in many countries,

Table 4. Anti-Coronavirus Therapy (ACT) trial primary and secondary outcomes

	Outcomes	
ACT trial	Primary	Secondary
Outpatient trial		
Colchicine vs no colchicine control	Hospitalization or death	Nil
Aspirin vs no aspirin control*	Major thrombosis, hospitalization, or death	Any thrombosis
Inpatient trial†		
Colchicine vs no colchicine control	High-flow oxygen, mechanical ventilation, or death	High-flow oxygen, mechanical ventilation, or respiratory death
Rivaroxaban plus aspirin vs no rivaroxaban plus aspirin control*	Major thrombosis, high-flow oxygen, mechanical ventilation, or death	High-flow oxygen, mechanical ventilation, or respiratory death Any thrombosis

* Major thrombosis includes myocardial infarction, stroke, acute limb ischemia, pulmonary embolism. Any thrombosis includes myocardial infarction, stroke, acute limb ischemia, or venous thromboembolism.

† Mechanical ventilation includes invasive or noninvasive ventilation.

Table 5. Examples of questions and requests for clarifications from regulators and ethics committees

Protocol
- The title of the protocol should include the place, the study population, the time, and the principal aim of the study.
- The protocol should contain a single aim for the outpatient and inpatient trials.

Design
- We do not agree with an open-label design.
- Please clarify the factorial design. Is the intent to have 4 treatment groups?
- The interpretation of these evaluations of each treatment that include comparisons where the other treatment is also being administered is unclear if that other treatment is not expected to be widely used in the proposed patient population (eg, if one treatment is found to be not effective and/or safe based on the results of this study).
- The proposed factorial analysis relies on an assumption of no statistical interaction between the treatments which may not be reasonable and, if violated, may lead to unreliable information on the effectiveness of the treatment.

Consent
- Clarify why verbal consent is proposed.

Randomization

Who is responsible for randomization? Please send details of procedures.

Interventions
- The committee questions the safety of long-term colchicine as it is usually given for a shorter period.
- Why test colchicine in mild disease?
- Are there any studies using aspirin and colchicine together? Will this combination work better than single use?
- The committee believes that the rivaroxaban and aspirin treatments in inpatients should be separated out.
- Clarify the goal of your development program and whether you intend to develop colchicine and ASPIRIN as a co-packaged combination therapy.
- Usual care is not well defined.

Follow up
- Telephone follow-up is inadequate for outpatients.
- We do not agree with your proposed follow-up schedule.
- Clarify in both protocol and informed consent, how follow-ups will be carried out on days 8, 45, and 6 months.

Benefits of participation
- What special measures will be taken to protocol the rights, well-being, and safety of subjects in a vulnerable situation (patients with COVID-19).
- How have the ethical principles of respect, justice, beneficence, and non-maleficence been applied in the selection of participants?
- Clarify who, when, how, and where the participants will receive the direct benefits of participating in the ACT trial.
- Possible benefits of the treatments are not well defined.
- There is an unfavorable benefit-risk ratio in this trial because the risks outweigh the benefits.

Statistical aspects
- Why is a 12% control event rate assumed? How is this percentage calculated?
- What statistical tests will be used to analyze the potential drug interactions?
- The ethics committee would like to analyze the country data after 50 patients have been recruited.

and by delays in importation of study drugs. Although regulatory and ethics delays were explained partly by the large number of new trial applications, the committees raised numerous questions, often reflecting a lack of understanding of the principles of randomized trial design and conduct, or misconceptions about their role in the oversight of clinical research (Table 5). These questions and comments pertained to the following areas:

1. trial design—confusion about the principles of a factorial design and interpretation of the results;
2. trial conduct—unwillingness to accept verbal consent and telephone follow-up, and the requirement that potentially infectious COVID-19 patients be seen face-to-face by study personnel;
3. interventions—failure to consider that most of the therapies under evaluation in the ACT trials were widely available, had been in clinical use for decades, and had safety profiles that were well established;
4. drug development—failure to recognize that academic sponsors had no intention of seeking new marketing approval for repurposed drugs that are shown to be effective;
5. equipoise—inappropriate assumptions about the net benefit of therapies under evaluation, reflecting lack of understanding of the principles of equipoise; and
6. administrative/other—how randomization would be performed, who would manage the database, and how statistical analyses would be performed (these were detailed in the protocol).

The preparation of detailed responses to address the hundreds of questions and comments took many hours and contributed substantially to delays in study start-up in many countries.

As the pandemic evolved, sensationalized media reporting, misleading claims by politicians, and conspiracy theories circulating on social media fueled community distrust and made patient enrollment even more difficult in many countries. At local sites, access by potential participants was limited by restrictions and lockdowns, and concerns about the risk of COVID-19 infection for site personnel added to the challenges. At the same time, the pandemic varied in its intensity in different regions of the world and even within countries. Where the pandemic was severe, clinical services were overwhelmed, and clinicians found it difficult to devote time for research; when the severity of the pandemic waned, fewer eligible patients were available. As a result, the trial initially experienced much slower than expected recruitment.

Protocol modifications

The rapidly changing pattern of the COVID-19 pandemic and emerging data regarding the efficacy and safety of novel therapies required several protocol modifications during the course of the ACT trials.

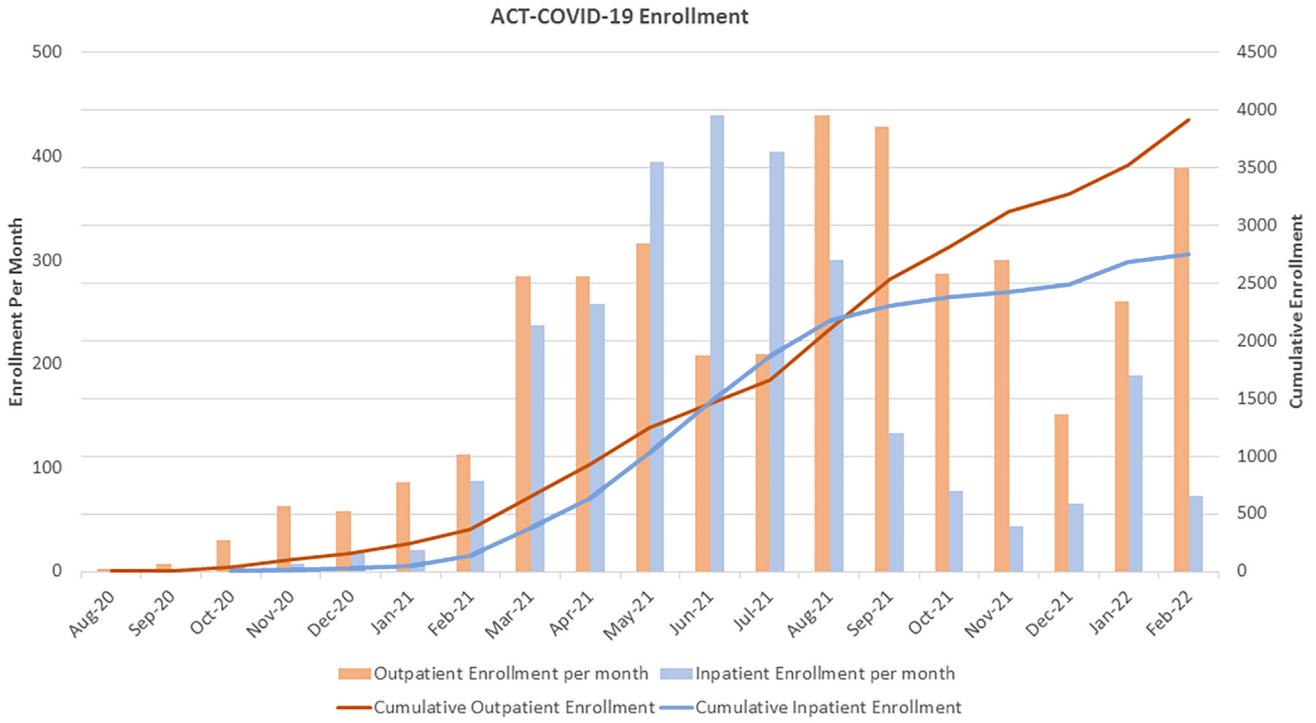

Figure 1. Anti-Coronavirus Therapy (ACT) trial recruitment rates during the COVID-19 pandemic.

As originally designed in April 2020, the ACT outpatient trial tested hydroxychloroquine or chloroquine in combination with azithromycin vs usual care, and the ACT inpatient trial used a 2 x 2 factorial design to test hydroxychloroquine or chloroquine plus azithromycin vs usual care, and beta-interferon vs usual care. In June 2020, evaluation of hydroxychloroquine or chloroquine in combination with azithromycin was discontinued in both the outpatient and inpatient trials because of data indicating no benefit from a large, randomized trial,[22] and ongoing concerns about the potential for harm. Patients enrolled in the initial phase of the ACT trials and who were randomized to hydroxychloroquine or chloroquine in combination with azithromycin, vs usual care, and interferon vs usual care, are not included in the current design, and their results are being reported separately. Randomizations to new treatments were added to both the outpatient trial, which began testing in a 2 x 2 factorial design colchicine vs usual care, and aspirin vs usual care, and the inpatient trial, which began testing in a 2 x 2 x 2 factorial design colchicine vs usual care, and combination of rivaroxaban and aspirin vs usual care, in addition to continuing beta-interferon vs usual care. In October 2020, beta-interferon was dropped from the inpatient trial because of emerging evidence that it did not provide benefit,[23] and ongoing concerns about safety.

In July 2021, further changes were made to the protocol based on an evaluation of blinded event rates. Although recruitment at this time was progressing at a rate of 300-400 patients per month in each of the outpatient and inpatient trials, the overall proportion of patients who had experienced a primary outcome was lower in both the outpatient trial (blinded overall event rates 6%-7%, vs 12% originally projected) and the inpatient trial (blinded overall event rates 15%, vs 30% originally projected). Furthermore, the proportion of outpatients under the age of 30 years who were experiencing a primary outcome was $< 2\%$. Accordingly, the steering committee (without knowledge of any emerging trends in the results) decided to increase the sample size in the outpatient trial (from 2500 to 3500) and the inpatient trial (from 1500 to 2500), modify the primary outcomes for the antithrombotic comparison in the outpatient trial (original primary outcome: hospitalization or death; revised primary outcome: major thrombotic events, hospitalization, or death), and in the inpatient trial for the colchicine comparison (original primary outcome: mechanical ventilation or death; revised primary outcome: requirement for high-flow oxygen, need for mechanical ventilation, or death) and the antithrombotic comparison (original primary outcome: mechanical ventilation or death; revised primary outcome: major thrombotic events, requirement for high-flow oxygen, need for mechanical ventilation, or death), and introduced a 30-year lower age cutoff in the outpatient trial.

ACT trials progress to date

Recruitment. At the completion of enrollment on February 10, 2022, the ACT trials had enrolled 3917 patients in the outpatient trial, and 2611 patients in the inpatient trial. The numbers enrolled varied markedly over the course of the trial, reflecting the changing patterns of the pandemic (Fig. 1).

Baseline characteristics. The baseline characteristics of the patients recruited into the trial are summarized in Table 6. In the outpatient trial, the mean age was 44.6 years (standard deviation 13.6), and 56.5% were male. In the inpatient trial,

Table 6. Anti-Coronavirus Therapy (ACT) trial—selected baseline characteristics*

Characteristic	ACT outpatient trial (n = 3917)	ACT inpatient trial (n = 2611)
Age, y, mean (SD)	44.6 (13.6)	56.5 (19.3)
Males	2191 (56.5)	1625 (59.2)
Diabetes	447 (11.5)	568 (20.7)
Hypertension	785 (20.2)	947 (34.5)
Coronary artery disease	130 (3.4)	91 (3.3)
Cerebral vascular disease	6 (0.2)	45 (1.6)
Active cancer	20 (0.5)	19 (0.7)

Values are n (%), unless otherwise indicated.

SD, standard deviation.

*At the time of writing, baseline data are not yet available for all patients enrolled in the ACT trials.

the mean age was 56.5 years (standard deviation 19.3), and 59.2% were male. Reflecting their younger age and less-severe illness, patients enrolled in the outpatient trial, compared with those enrolled in the inpatient trial, generally had fewer cardiovascular comorbidities (diabetes: 11.5 vs 20.7%; hypertension: 20.2 vs 34.5%; cerebrovascular disease: 0.2 vs 1.6%, and active cancer 0.5 vs 0.7%).

Discussion

The ACT trials are testing whether anti-inflammatory therapy with colchicine and antithrombotic therapy with aspirin in outpatients, or the combination of rivaroxaban and aspirin in inpatients, can reduce major thrombotic events, hospitalization, need for high-flow oxygen, need for mechanical ventilation, and mortality.

The promise of colchicine suggested by the results of the COLCORONA trial in outpatients (primary outcome: relative risk 0.79, $P = 0.081$),[10] and those of the COLCOVID trial in inpatients (primary outcome: relative risk 0.83, $P = 0.08$)[11] was not supported by the results of the larger RECOVERY trial (primary outcome: relative risk 1.01, $P = 0.77$)[12] of inpatients with COVID-19. Whether differences in the severity of COVID-19 may have influenced the apparently divergent results of the inpatient trials is unclear, but comparison of mortality rates in the COLCOVID trial conducted in Argentina (21%), and the RECOVERY trial conducted in the UK (21%), suggest a similar risk profile. One possibility is that a longer duration of colchicine treatment, as evaluated in the COLCORONA trial (30 days) and the COLCOVID trial (up to 14 days,) is more effective than up to 10 days of treatment as in the RECOVERY trial. Although colchicine works rapidly, and in previous trials most events occurred within the first 7 to 14 days after randomization, patients may benefit from extended treatment because evidence indicates a prolonged inflammatory state in patients with COVID-19. Finally, the widespread use of glucocorticoids (> 90% in both inpatient trials) could have masked any potential benefit of colchicine. The ACT trial is well positioned to further inform the potential efficacy of use of colchicine, which is being tested for up to 28 days across the spectrum of mild, moderate, and severe disease, and in populations more diverse than those previously studied.[24,25]

The lack of convincing evidence from randomized trials of a net benefit of antithrombotic therapy in patients with COVID-19 has several possible explanations. The largest completed trial to date involved 2219 inpatients,[26] and although VTE event rates were generally lower with the use of intensified antithrombotic therapy, most of the differences were not significant and were accompanied by increases in bleeding, with no mortality benefit. In the **A**nti**c**oagula**ti**on C**o**r**on**avirus (ACTION) trial involving hospitalized patients with COVID-19, therapeutic anticoagulation with rivaroxaban 20 mg once daily (or therapeutic parenteral anticoagulation in those who were unstable) was not more efficacious than prophylactic anticoagulation, and it increased bleeding.[27] The lower 2.5 mg twice daily dose of rivaroxaban being tested in combination with aspirin in the ACT inpatient trial was chosen because of proven efficacy in previous trials for the prevention of both venous and arterial thrombosis.[19,28] Furthermore, by targeting both platelets and fibrin, this combination has the potential to prevent microvascular thrombosis and related organ dysfunction in patients with COVID-19.

Investigator awareness of treatment allocation in an open-label trial could affect decisions about patient management (eg, non-study treatments for COVID-19, decisions regarding hospitalization) and may also influence ascertainment and reporting of outcomes. To address these issues, we will compare the use of cointerventions and the severity of illness at the time of hospitalization by treatment group. To further mitigate risk, we provide objective criteria for study outcomes, and we monitor data quality, including the reporting of outcomes.

The COVID-19 pandemic has resulted in unprecedented challenges in the conduct of randomized trials, owing to community lockdowns, hospital restrictions, difficulties in procuring investigational products, and risks of COVID-19 infection for site personnel, as well as changing COVID-19 disease patterns around the world. Further compounding these issues, investigators faced challenges from lack of reliable data to support hypothesis testing and uncertainty about event rates. Regulatory and ethics delays were exacerbated by the large number of trials that had to be reviewed, and recruitment was delayed by competition between trials for patient enrollment at individual sites. Lessons learned from these experiences should inform future planning of clinical trials, especially when a new pandemic disease arises, with a focus on large, pragmatic, collaborative, efficient trials, with flexible adaptive designs that are integrated into routine clinical care.[29]

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2022.02.010.