Covid19 Treatment with Hydroxychloroquine and Zinc: Collaborative Database and Fast-track Crossover Trial Design for Expedited Evaluation

Currently the efficacy of Hydroxychloroquine (HCQ) is hotly debated. Several doctors claim success with HCQ together with zinc. Research has shown that HCQ increases zinc uptake into cells, and that zinc blocks virus replication.\(^1\) Thus HCQ+Zinc therapy shows promise and plausibility, yet is still ignored or greeted with skepticism, due to a lack of the hard empirical data normally expected for a new treatment.

HCQ has shown uneven results in earlier studies. We hypothesize that HCQ works by making zinc more bioavailable, so it needs to have enough free serum zinc to work with. "Bioavailability studies are usually conducted as crossover studies."\(^2\) Thus we propose a short longitudinal trial to determine the efficacy of HCQ with and without zinc. Trials may need some flexibility, as acute care for patients comes first.

An ideal way to quickly gather retrospective and new trial data can be to enlist independent physicians who are currently treating coronavirus patients. An estimated 60% of physicians worldwide have prescribed HCQ, but fewer than 20% have added zinc, and even fewer prescribe high-dose zinc. Yet if the zinc ionophore thesis and field reports are valid, high-dose zinc should be prescribed as often as its auxiliary HCQ.

### Existing Data
Solicit datasets and papers from practitioners who have been prescribing HCQ and zinc, typically along with Zpack, vitamins, Ivermectin, etc.

### Trial design for controlled data
Inclusion: Coronavirus patients, any setting, from mild to critical condition.
Exclusion: No HCQ where contraindicated.
All patients get standard dose HCQ (e.g. 2x 200 mg loading dose then 200 daily) for the entire study, e.g. 10 days. The simplest trial is to have each patient on zinc or no zinc/placebo on alternating periods of 3 to 5 days, and compare progress of symptoms between the zinc and placebo periods. Larger groups of patients can be divided into two, which take turns getting high dose zinc (approx. 5 times the daily requirement, e.g. 220 mg zinc sulfate). Where practical, give a placebo when not on zinc.
For outpatients, record their condition at the start and end of each period. Serum zinc should also be measured at these intervals if possible. When zinc level testing is not available, trials could eventually be done remotely, with self-reporting of symptoms and even mailing of follow-on tablets to patients.
Already after the first period the trend in condition can be compared between the zinc and no-zinc groups. After two or more periods, the change in condition with and without zinc can be compared more precisely for each patient.

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\(^1\) [https://www.researchgate.net/post/Is_a_combo_of_chloroquine_and_Zinc_a_cure_for_coronavirus](https://www.researchgate.net/post/Is_a_combo_of_chloroquine_and_Zinc_a_cure_for_coronavirus)

\(^2\) [https://www.sciencedirect.com/topics/neuroscience/crossover-study](https://www.sciencedirect.com/topics/neuroscience/crossover-study)
This is a practical test that mirrors the usual way doctors proceed, trying different medications to see what works. At the same time, the design produces objective data that third parties can use to assess and validate the results.

The trial can be double blind in research hospitals, but need not be in private doctor's offices. The study can include an arm with a half dose of zinc given for the full period, while alternating HCQ vs. placebo.

It is intended for the trial design to be simple, inexpensive and flexible. It can be modified to suit, to assess the efficacy of different zinc compounds, different ionophores (for instance those not requiring a prescription), and compounding or complexing the zinc with its ionophore directly in tablets.

Assignment to first or second group can be randomized by alternating assignment to groups as patients come in. Higher risk patients can be assigned to zinc in the first period.

The design doesn't put any patient at a disadvantage by getting placebo only. This makes it more ethical and easier to recruit subjects. Patients continue on Standard of Care and their usual medications; HCQ and zinc are merely added to that. Ethical and regulatory issues are minimal, since no new drug is being developed. HCQ is on the WHO list of safe, essential medicines, but at intake an EKG may be given to allay concerns about rare instances of arrhythmia. Treatment should normally covered by insurance, and the extra effort of the trial format may be compensated by increased local goodwill for participating doctors.

The primary aim of the proposed trial model is not to maximize statistical rigor. It is a vehicle for hospitals and physicians to share their experiences with a promising therapy with each other and the community, and to validate or refute the claims for it, so as to help meet the challenges we face.