Pursuing Evidence Ethically for COVID-19

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Outline

The need for research
Beyond "research ethics" to ethical research
Communication ethics
Case 1: Ivermectin
Case 2: Hydroxychloroquine
Case 3: Remdesivir
Seeking wisdom in the weeds

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Uncertainty Abounds

"There are currently no antiviral drugs with proven clinical efficacy, nor are there vaccines for its prevention, and these efforts are hampered by limited knowledge of the molecular details of SARS-CoV-2 infection."

Gordon et al. *Nature* doi: 10.1038/s41586-020-2286-9

What should policy-makers do?

What should clinicians recommend?

What should we all do?

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Ethical Imperative for Research

"Conducting research is linked to 'a moral obligation to learn as much as possible, as quickly as possible'. … research – implemented as policy and practice – can save lives."

WHO. *A Coordinated Global Research Roadmap: 2019 Novel Coronavirus*. March 2020 https://bit.ly/2NjlA1I

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Pursing Evidence

involves

Conducting Research

and

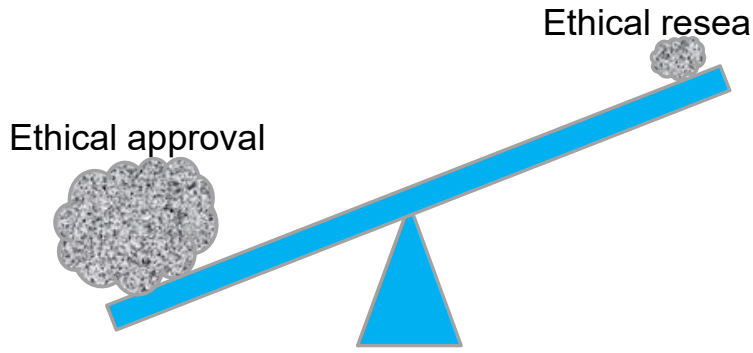
Communicating Results

and

Critically appraising Reports

All done ethically

Research Ethics or Ethical Research?



O'Mathúna D, Siriwardhana C. Research ethics and evidence for humanitarian health. *Lancet* 2017;390(10109):2228-2229.

O'Mathúna DP. The dual imperative in disaster research ethics. In: *SAGE Handbook of Qualitative Research Ethics*, eds. Iphofen R, Tolich M. 2018; 441-454.

What Sort of Research … in a Crisis?

"In critical situations, large randomized controlled trials are not always feasible or ethical, and critically ill patients may need to be treated empirically during times of uncertainty.

Hence, small sample sizes, unvalidated end points, non-random allocation, and blinding "may be acceptable."

Kim AHJ, et al. *Annals of Internal Medicine* 2020;172(12):819-821.

"But with speed borne of desperation comes risk and confusion—of trials too small to yield answers, of treatments overhyped, and of uncertainty about how to design the best studies possible."

Couzin-Frankel J. *Science* 16 June 2020 doi:10.1126/science.abd3588

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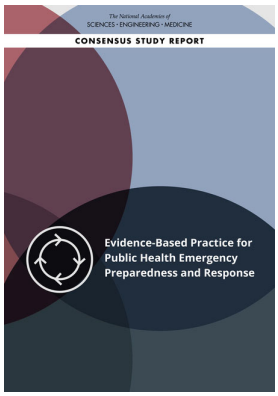
"Qualitative and quantitative evidence may both contribute to understanding an intervention or practice and ultimately what works" (3-5).

http://nap.edu/25650



"We have to do our best science to make sure that we answer the questions as definitively as possible."

Different questions require different methods.

Flexibility where appropriate.

Couzin-Frankel J. *Science* 16 June 2020 doi:10.1126/science.abd3588

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Balancing Ethical Priorities

If overly cautious: clinical development will be impeded or delayed, and leave more patients without treatments for longer.

If insufficiently cautious: patients will be exposed to unknown risks and resources will be diverted to ineffective treatments or more reasonable options.

"In both cases, misestimation threatens the integrity of the scientific enterprise, because it frustrates prudent allocation of research resources."

Kimmelman J, London AJ. *PLOS Medicine* 2020;8(3):e1001010.

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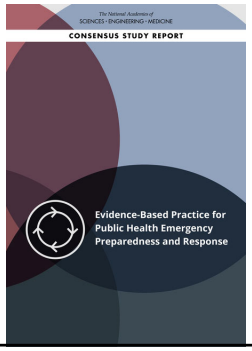
Racing for Results

"There are no winners in these races if harm—even though unintentional—is wrought by the dissemination of hurried, incomplete, biased misinformation."

Saitz R, Schwitzer G. *JAMA* 13 July 2020 doi: 10.1001/jama.2020.12535

Good communication "has *intrinsic* value" as transparency promotes "respect for persons and communities" (6-13).

http://nap.edu/25650



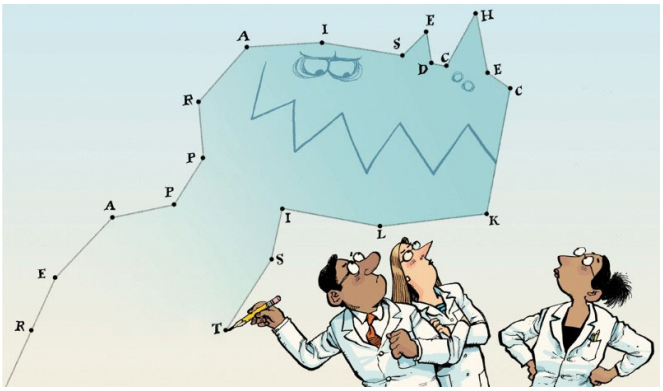
REAPPRAISED checklist

Publication integrity: reliability and validity, not misconduct

Series of questions in 11 categories:

- understanding research
- common sense

Grey et al. *Nature* 2020;577:167-9. https://www.nature.com/articles/d41586-019-03959-6



http://prores-project.eu/

PRO-RES

London AJ, Kimmelman J. *Science* 2020;368(6490):476-7.

Case 1: Ivermectin

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Image: Davey M. *The Guardian* 4 June 2020 https://bit.ly/30VAKIK

Antiparasitic; FDA-approved orally for parasitic worms; topically for headlice and rosacea; animal use; 2.5 billion doses – excellent safety record

Newsweek

NEWS

Anti-Parasite Drug Used Since 1980s May Help Stop Coronavirus, New Study Says

BY AILA SLISCO ON 4/3/20 AT 10:46 PM EDT

Chaccour C, et al. *Am J Trop Med Hyg* 2020;102(6):1156-7.

Caly L, et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*. *Antiviral Research* 2020;178:104787.

But… at 10x the FDA-approved dose, it was not effective *in vitro*.

Effective at 50-100x peak plasma conc after usual human dose.

Inhibits in lab single-stranded RNA viruses, e.g. dengue, Zika, yellow fever

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Rapid Publishing

In vitro study triggers widespread use in Latin America → shortages

10 April: FDA warns about using veterinary products

Caly et al. *Antiviral Research* 2020;178:104787

6 April: SSRN preprint based on Surgisphere database: ivermectin strongly associated with improved survival of COVID-19 patients on ventilators: 7.7% death rate (n=52) v. 18.6% not receiving ivermectin (n=1,900)

20 April, version 2: 704 case-control analysis: 1.4% v. 8.5%

Patel AN, Desai SS, Grainger DW, Mehra MR. *SSRN* 6 April 2020 https://bit.ly/318Z97t

Patel AN, Desai SS, Grainger DW, Mehra MR. *SSRN* 20 April 2020 https://bit.ly/3hXJnC6

Ethical Dilemmas

Peru's Health Minister didn't have time "to wait for scientific evidence."

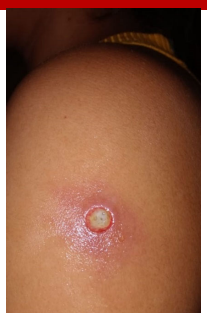
South American tropical medicine expert: "what do you do? … Give them water?"

May 8: Ivermectin added to COVID-19 clinical guidelines in Peru

May 12: in Bolivia; later Brazil, Chile

Offord C. *The Scientist* 16 June 2020 https://bit.ly/3hIFqkX

Consequences



Veterinary formulations led to adverse effects, e.g.:

Doctors pressured by patients to give them ivermectin.

RCTs more challenging, especially with placebos.

Eventually:

"I think people have lost faith in science… and it has been very, very bad for us in Latin America" (Patricia Garcia, Peruvian global health researcher).

Offord C. *The Scientist* 16 June 2020 https://bit.ly/3hIFqkX

A Deeper Dive

Carlos Chaccour: Venezuelan physician and researcher; worked in the Amazon and with Ivermectin for 12 years: "It was so weird."

Surgisphere paper	Reality
52 patients on ivermectin	Ivermectin not widely known
3 patients on ventilators in Africa	Only 2 COVID-19 cases known in African (3rd identified later) – none serious
	Most African hospitals didn't have the electronic systems Surgisphere used
Death rate among US ventilator patients: 2%	*JAMA* reported death rate in NY: 25%

Davey M. *The Guardian* 4 June 2020 https://bit.ly/30VAKlK

Offord C. *The Scientist* 16 June 2020 https://bit.ly/3hIFqkX

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Systematic Review

Antimicrobial, antiviral, anti-cancer "wonder drug."

50 years of widespread *in vitro* activity against many viruses "has not been reproduced in mouse infection models … and has not been clinically proven either."

- pharmacokinetics and safety

Heidary F, Gharebaghi R. *Journal of Antibiotics* 12 June 2020 10.1038/s41429-020-0336-z

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Case 2: Hydroxychloroquine and Chloroquine

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Image: Grady D. *NY Times* 1 Apr 2020 https://nyti.ms/2NnibyW

FDA-approved to treat or prevent malaria. HCQ approved for autoimmune conditions like lupus, rheumatoid arthritis. Emergency use authorization for hospitalized COVID-19 patients. FDA. 24 April 2020 https://bit.ly/3hUc1Ea

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The French Connection

20 March: 42 patients, open-label, non-randomized study

Gautret P, et al. *Int J Antimicrob Agents* doi: 10.1016/j.ijantimicag.2020.105949

PI Didier Raoult: "dictatorship of the methodologists" Sciama Y. *Science* 9 April 2020 https://bit.ly/3dqTT1m

Presidential involvement and public support

460,000 sign French petition for access: former Minister for Health; infectious disease expert, Prof Christian Perronne: refused to do RCTs because a placebo was "unethical" for a fatal disease. Uses HCQ widely.

Davey M. *The Guardian* 4 June 2020 https://bit.ly/30VAKlK

Convoluted Controversy

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1 May: *NEJM* study: Surgisphere database: 8910 patients in 169 hospitals in 11 countries; heart patients have higher risk of death

Mehra MR, Desai SS, et al. *NEJM* 1 May 2020 doi:10.1056/NEJMoa2007621

22 May: *Lancet* hydroxychloroquine study: 96,000 Surgisphere pts in 1200 hospitals; HCQ increased risk of heart problems and deaths

Mehra MR, Desai SS, et al. *Lancet* 22 May 2020 doi:10.1016/S0140-6736(20)31180-6

23 May: WHO halted hydroxychloroquine arm of Solidarity trial; 131 other trials registered, and many halted.

"Its findings, to many, seemed definitive." Davey M. *The Guardian* 4 June 2020 https://bit.ly/30VAKIK

Offord C. *The Scientist* 16 June 2020 https://bit.ly/3hIFqkX

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However…

More Australia data than there were patients – correction in *Lancet*.

Desai: "The real question here is, with data like this, do we even need a randomised control trial?" Bigger questions Davey M. *The Guardian* 4 June 2020 https://bit.ly/30VAKIK

2019: from medical textbook publisher to data analytics and AI.

Media investigation: no Australian hospital knew Surgisphere.

- How did the hospitals have time to de-identify patient data?
- How was the data being uploaded and synced?
- Data on race reported for countries where not collected

June 4: *NEJM* and *Lancet* articles retracted.

Ongoing questions about Desai's career Davey M, Kirchgaessner S. *The Guardian* 10 June 2020 https://bit.ly/3hGDSba

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Communication Ethics

"It is incumbent upon the publisher, editors, authors, and readers to ensure that the highest standards of scientific scholarship are upheld."

Desai SS, Shorttell CK. *J Vascular Surgery* 2011;54:59S-63S

"Rushing publication, if there are mistakes, will ultimately undermine public trust in science."

Bauchner et al. *JAMA* 26 June 2020; doi: doi:10.1001/jama.2020.11764

Back on the Roller Coaster

The New York Times

Malaria Drug Helps Virus Patients Improve, in Small Study

Chen Z, et al. *MedRxIV* doi: 10.1101/2020.03.22.20040758

A group of moderately ill people were given hydroxychloroquine, which appeared to ease their symptoms quickly, but more research is needed.

By Denise Grady April 1, 2020

"It's going to send a ripple of excitement out through the treating community," said Dr. William Schaffner, an infectious disease expert at Vanderbilt University. But…

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Trial Registration and Protocols

	Protocol	Pre-print Report
Patients	30-65 years old	Over 18 years
Groups	3 groups of 100 people (100 mg bid; 200 mg bid; starch pill)	2 groups of 31 (200 mg bid; standard care). No power analysis
Blinding	Double-blind	No placebo mentioned
Randomization	"method of stochastic indicator of group"	"a computer-generated list stratified by site"
Outcomes	Time to negative SARS-CoV-2 test; blood lymphocyte values	Time to recovery of body temp or cough, or to severe illness; chest CT comparisons

Ferner RE, Aronson JK. CEBM https://bit.ly/2Nj5PaR

Single Trials vs. Accumulating Evidence

27 May: Meta-analysis of 24 small studies: very weak & conflicting evidence
Hernandez AV, et al. *Ann Int Med* 27 May 2020 doi: 10.7326/M20-2496

5 June: RECOVERY trial: 11,000 patients, 175 UK hospitals, RCT with 6 drug arms + placebo: Based on 4674 in HCQ or placebo: "These data convincingly rule out any meaningful mortality benefit."
RECOVERY 5 June 2020 https://bit.ly/2YrtnRh

8 June: Postexposure prophylaxis (PEP) studies in Minnesota and Barcelona: no benefit
Thomas K. *New York Times* 20 June 2020 https://nyti.ms/2B3557b

17 June: WHO stops hydroxychloroquine arm of Solidarity trial

17 June: FDA revokes emergency use authorization
Geleris J. *NEJM* 2020;382:2411-8

18 June: observational study, 1446 NY patients

20 June: NIH stops large ORCID RCT: no benefit, no harm
NIH. 20 June 2020 https://bit.ly/2CuMxxj

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Clinical Ethics and Evidence

"Given the toll of COVID-19, the pressure to do something is enormous and understandable… As health care providers, we should inform patients about the evidence behind experimental therapies, work to enrol patients in randomized clinical trials, and consider the needs of patients without COVID-19 who may be effected by drug shortages… Although we may be tempted to bypass enduring principles in this time of uncertainty and fear, the best way to protect patients is to stay grounded in evidence and to fight misinformation."

DeJong C, Wachter RM. *JAMA* doi:10.1001/jamainternmed.2020.1853

These drugs have already been used by "hundreds of thousands of patients, but with scant evidence about the risks and benefits."

Rubin EJ, et al. *NEJM* 2020;382(25):2461-2.

Isn't something better than nothing?

Chloroquine recommendation: 600 mg twice daily x 10 days = high-dose arm (13 g total)

Compared with 450 mg twice on Day 1, then once daily x 4 days = low-dose arm (2.7 g total)

Placebo viewed as unethical: compassionate use and media pressure

Planned sample size: 440; after 81 patients, study stopped:

- High-dose: lethality, 39.0%; QTc adverse effect, 18.9%
- Low-dose: lethality, 15.0%; QTc adverse effect, 11.1%
- Mortality rate: not lower compared to historical cases

Borba et al. *JAMA Network Open* 2020;3(4):e208857.

Case 3: Remdesivir

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Image: Grady D. *NY Times* 1 Apr 2020 https://nyti.ms/2NnibyW

Antiviral not FDA-approved. Developed for Ebola; some promise for SARS and MERS in animal studies. Emergency use authorization for hospitalized COVID-19 patients. FDA. 24 April 2020 https://bit.ly/3hUc1Ea

In vitro and animal studies showed potential.

ACTT-1: randomized, double-blind, placebo trial of IV remdesivir in adults hospitalized with COVID-19 with respiratory problems

60 trial sites in 10 countries

Beigel JH, et al. *NEJM* 22 May 2020 doi:10.1056/NEJMoa2007764

After 1063 participants, data & safety monitoring board stopped trial

Changed primary outcome: recovery: 15 days, placebo; 11, remdesivir

Trend to lower mortality: 11.9% placebo; 7.1% remdesivir

Those on ventilators: no benefit.

Saitz R, Schwitzer G. *JAMA* 13 July 2020 doi: 10.1001/jama.2020.12535

"Conducting such a clinical trial only a few months after SARS-CoV-2 was discovered is an extraordinary achievement."

Dolin R, Hirsch MS. *NEJM* 27 May 2020 doi:10.1056/NEJMe2018715

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Ethical Issues

Usual RCT ethical issues with severely ill patients.

Also, resource allocation issues when little drug was available.

Tiered access based on symptoms and drug availability.

Criteria changed with changing evidence (e.g. 5 versus 10 day treatment)

Goldman JD, et al. *NEJM* 27 May 2020 doi:10.1056/NEJMoa2015301

"Solidarity" clinical trial for COVID-19 treatments

Coordinated by the World Health Organization (WHO)

Adaptive trial design: random allocation to 1 of 5 groups; patients and clinicians blinded; doses, drugs, groups, etc. can be adapted based on accumulating evidence reviewed by independent DSMB.

4 treatment arms: Hydroxychloroquine, Remdesivir, Lopinavir/Ritonavir, Lopinavir/Ritonavir + Interferon beta-1a

3 June: >3,500 patients at 400 hospitals in 35 countries with over 100 countries interested in becoming involved.

In 60 countries, WHO assists with IRB, training, ship drugs

17 June: Hydroxychloroquine arm ended

WHO. June 2020 https://bit.ly/314AYXA

Ethics Conclusions

Transparency: patients should be informed if interventions are unapproved, uncertain, experimental, etc.

Rigor: controlled studies are needed to answer effectiveness questions.

Flexibility: what can be changed?

Honesty: data should be collected and disseminated accurately.

Diligence: all reports must be appraised carefully, including peer-reviewed ones, but especially pre-prints, press releases, and other media.

Assess harm broadly: from hoarding & diverting drugs to issues of trust.

Justice and fairness: disparities, allocation decisions, global implications.

Humility: keep to the facts, acknowledging limitations, and admitting that if we don't know, we don't know.

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Thank you

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