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Centre for Biomedical Ethics
Yong Loo Lin School of Medicine

CBmE PANDEMIC ETHICS SERIES

Experimental and Non-Standard Interventions for COVID-19

Working Paper 6

This working paper is part of a series written by the Centre for Biomedical Ethics, Yong Loo Lin School of Medicine, National University of Singapore, and is intended to provide information for healthcare professionals and decision-makers on ethical issues arising from the COVID-19 pandemic. The views expressed do not, in themselves, reflect official government policy on these matters. Contributors to the series are listed on the last page.

REFERENCES

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2. National Centre for Infectious Diseases, Singapore. Interim Treatment Guidelines for COVID-19, Version 4.0. Available at: https://www.ncid.sg/Documents/Interim%20Treatment%20Guidelines%20for%20COVID-19%20v4%20%2831%20Aug%202020%29-%20final.docx%20for%20upload.pdf.

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CBmE PANDEMIC ETHICS SERIES

Experimental and Non-Standard Interventions for COVID-19

When is it ethically acceptable to provide non-standard, non-indicated or experimental interventions to COVID-19 patients?

This document aims to guide physicians responding to requests for interventions that are not routinely being used to treat COVID-19 patients in Singapore and to make decisions to offer such interventions outside the standard care.

These recommendations are meant as a guide and should be contextualized to the particular details of the cases encountered in practice. They are consistent with the Singapore Medical Council Ethical Code and Ethical Guidelines (SMC ECEG), ethical guidance from the World Health Organisation (Monitored Emergency Use of Unregistered and Investigation Interventions, or MEURI) on using unproven interventions during infectious disease outbreaks, and the Mental Capacity Act (MCA).

Key Ethical Principles

1	Beneficence and non-maleficence	The obligation towards persons (particularly physicians towards their patients) to prevent and minimize harm, and promote their interests and well-being.
2	Equity	Treating individuals and groups fairly based on equal respect.
3	Population health	Safeguarding the overall health of the population in Singapore.
4	Respect for persons	An obligation towards the self-determination of persons to be fully informed of material risks and benefits prior to voluntarily consenting or refusing any intervention in clinical care. Where persons lack capacity for self-determination, the principle extends to the decision-maker who may refuse or consent to an intervention on the patient's behalf in accordance with the patient's best interests.
5	Solidarity	The commitment among persons with recognised morally relevant sameness or similarity to sharing costs and benefits for the good of a group, community, nation, or global population.

This guidance considers two types of therapeutic interventions:

Type A	Off-label use of a standard intervention or product licensed by the Health Sciences Authority (HSA) that is not indicated for the treatment of COVID-19, OR use of an unlicensed product with the potential for efficacy in treatment of COVID-19.
Type B	An experimental or innovative intervention for which there is little/scant evidence of efficacy or safety; and that is not currently being investigated in a study approved by an Institutional Review Board (IRB).

Some interventions may be categorized as both Type A and Type B, and in such cases, the guidance for both would apply.

Type A interventions

(off-label, non-indicated, non-standard or unlicensed)

1. The SMC ECEG describes the physician's responsibility in the context of off-label use of any treatment, viz:

   "If you use "off-label" drugs, you must ensure that it is in the patients' best interests, there is rational basis, patients have justifiable medical indications, you have assessed the risks and benefits of such use and patients' consent to such use has been obtained if they are able to give it" (SMC ECEG Section B5 (9)). In addition to proper documentation of consent, patients "should be appropriately monitored for effectiveness and side effects". (SMC Handbook on Medical Ethics).

2. According to the SMC ECEG, "*when variances from standard use are so significant that they render the techniques novel and unclear in their risk profiles* (SMC Handbook adds; "*or significantly increase the degree of ignorance of risk*"), these treatments become not generally accepted (or non-standard). In such cases, "*the treatments must be offered to patients only in the context of formal and approved clinical trials which would be subject to the ethics of research*" (para B6). Exception is made in the case of innovative therapy (see section Type B interventions below).

3. Limiting access to non-standard interventions to patients enrolled in an IRB-approved study is consistent with the values of equity, non-maleficence and population health. Health authorities have an obligation to ensure that populations and patient groups have access to safe and efficacious treatment that has gone through a systematic process of testing. Well-designed studies with fair selection methods can more efficiently contribute to the emerging evidence-base needed to systematically evaluate the safety and effectiveness of these intervention for treating COVID-19.[1] IRB review also provides additional safeguards to protect patient safety in the context of greater uncertainty over risks and benefits characteristic of unproven interventions.

4. The use of unlicensed interventions requires prior approval from the relevant authorities. The provision of an unlicensed product to patients without authorisation from the HSA may breach the Medicines (Clinical Trials) Act and/or Health Products Act. The HSA has a Special Access Route that licensed hospitals, clinics and pharmacies can use to apply to import and provide an unlicensed investigational product for a specific, individual patient for life-saving treatment for which there is no alternative registered therapy available.[2] HSA states explicitly that it does not evaluate these products for quality, efficacy and safety; and the full responsibility for use of such a product, once approved, lies with the requesting doctor. SMC ECEG expects that doctors will base this use on the patient's best interests and act only with express consent by the patient or their next-of-kin. (SMC ECEG para B5 (10)).

5. Beyond the provisions by regulatory authorities and in the SMC ECEG regarding the use of these interventions for individual patients, any Type A intervention that is systematically offered to a series of patients meeting defined criteria should be made the subject of an IRB-approved clinical trial at the earliest opportunity. A surge in non-standard interventions being made available to COVID-19 patients on an individual basis may preclude or delay the initiation of well-designed clinical trials that could contribute to an evidence-base on safety and efficacy.[3] This outcome may unfairly deprive physicians and future patients of benefits that may be generated from the completion of clinical trials that can support the registration of safe and effective products to treat COVID-19.

[1] London AL & Kimmelman J. Against Pandemic Research Exceptionalism. *Science* 368, 476–477 (2020). Available at: https://doi.org/10.1126/science.abc1731.

[2] HSA guidance document (updated 2 Jan 2020) on the Import and Supply of an Unregistered Therapeutic Product for Patient's Use. Available at:https://www.hsa.gov.sg/docs/default-source/hprg-tpb/guidances/tpb-gn-004-002-import-and-supply-of-an-unregistered-therapeutic-product_2-jan-2020.pdf.

[3] Manufacturers may only have limited supplies of the product, which may be under increased pressure with international transportation routes freezing up as a result of the pandemic. They may also become disincentivised to invest in the registration and clinical trial process if the product is made available to patients, who may in turn become reluctant to enrol in formal clinical trials if they are able to access products without the risk of being randomly allocated to a control arm. See Lynch, H.L, Bateman-House, A., & Caplan, A. L. (2020). 'Panic Prescribing' Untested Coronavirus Treatments: A Danger To Patients Today and Tomorrow. Health Affairs Blog. March 31. Available at: https://www.healthaffairs.org/do/10.1377/hblog20200330.265604/full.

Type B interventions

(experimental / innovative)

1. The provision of completely novel or significantly modified standard interventions with an insufficient level of evidence of safety or efficacy ('innovative therapy') may be justified outside the context of an IRB-approved study in exceptional circumstances.

2. The SMC ECEG provides guidance for the use of innovative therapy, viz, when all other options have been considered and deemed unhelpful, and in a desperate or dire situation.

   A. COVID-19 patients with severe disease[4] for whom the intervention provides the opportunity for saving of life or amelioration of intolerable pain and suffering, and who are not able to enrol into an IRB-approved study for any reason, may be judged to be in a sufficiently dire situation to justify providing the intervention solely as part of the individual patient's clinical care.

   B. COVID-19 patients who are known to be at high risk of progressing to severe disease (based on other epidemiological indicators) but whose clinical condition is mild/moderate may be candidates for innovative interventions in the context of a pandemic. This is justified by the potential that they may contribute to an unmanageably large numbers of severely ill patients whose needs (e.g. for ICU care) would overwhelm existing healthcare resources. Treatment of such patients at a stage in the disease that would avert a desperate situation for society as a whole, could potentially be considered as fulfilling the criteria above. The systemic benefit to risk ratio calculus in such cases should also take into consideration the need for resources to treat potential side effects if they arise. In such cases, (a) the impact on the system should be established and (b) it must be clear that the individual patient's best interest is served by early intervention, and the potential risks to the individual associated with the treatment are materially lower than the likelihood of averting progression to a severe state.

[4] As defined in the Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) February 2020, and adapted in the NCID Interim Treatment Guidelines for COVID-19 (Version 1.0, dated 2 April 2020).

3. The use of such interventions for individual patients should be governed by the SMC ECEG and guided by national and international guidelines, viz:

   A. There should be consensus among relevant professionals on a favourable benefit to risk ratio in the patient's specific clinical context. Institutions/relevant authorities should have in place specific requirements for notification of such plans for approval/ acknowledgment. When national and/ or international therapeutic guidelines have set out a *priori* eligibility criteria, the physician may proceed to offer the innovative intervention after complying with existing institutional requirements and obtaining informed consent from the patient. Where the guidance documents are silent on a particular intervention, the physician will provide to the Institution or Clinical Ethics Committee, on a case by case basis, a written plan outlining treatment goals, the system for monitoring and reporting outcomes, and exit criteria. Consideration of these requests should be expedited.

   B. In an emergent situation where the requirements in section 3a above cannot be met, at least one other professional opinion (from a specialist in a relevant field of practice) that the treatment is in the patient's best interest in the specific clinical context should be obtained and documented.

   C. Consent from the patient or their next-of-kin if the patient lacks mental capacity to give consent should be secured, based on relevant information on the uncertainty regarding probability of benefits and adverse outcomes.

   D. Proper documentation should be maintained.

   E. Adequate resources should be available to minimize risks.

   F. In line with SMC ECEG and MCA, make efforts (to the degree practicable, given social distancing measures) to solicit input from the family, carers and/or legally appointed representatives on the values and perspectives of the patients concerning such interventions or products (if ascertainable).

4. If the proposed goals are achieved, making the intervention subject of an approved IRB study as soon as practical is aligned with the values of population health, equity, nonmaleficence, solidarity and beneficence for future patients.

Special considerations for minors and adults lacking decision-making capacity

1. Where the patient is a minor or an adult who lacks decision-making capacity and the family demands access to Type A or B interventions, the considerations on whether to offer the intervention to the patient will be similar as in any other clinical context.

2. For adults lacking mental capacity, the Mental Capacity Act (MCA) and SMC ECEG will still apply. Prioritizing the values of beneficence and non-maleficence, any decision to attempt one of these interventions on COVID-19 patients lacking decision-making capacity to consent rests with the care team, who must:

   A. Determine whether said intervention is clinically indicated and in the patient's best interests, and

   B. In line with SMC ECEG and MCA, make efforts (to the degree practicable, given social distancing measures) to solicit input from the family, carers and/or legally appointed representatives on the values and perspectives of the patients concerning such interventions or products (if ascertainable).

3. While the decision ultimately rests with the care team, they should involve the family in their decision-making process. The family's input on the non-clinical factors and the care team's input on the clinical factors that impact the patient's best interests should be considered together to come up with a decision that is in the patient's overall best interests.

4. However, in the case of experimental or nonstandard interventions, the evidence base for potential benefit will, by definition, be poor. Because the patient is unable to critically evaluate for themselves whether the highly uncertain benefits are worth any risks involved, the care team should be especially cautious before proceeding. It would be ethically permissible to proceed with a given intervention in an adult who can provide informed consent, but may be inadvisable to do so for an adult lacking the ability to consent.

5. Similarly, for minors (patients below the age of 21), the prevailing recommendations of the SMC ECEG should be abided by. Commensurate with the minor's level of maturity, this includes effectively communicating with the patient and seeking to understand their perspective.

6. While a standard intervention may be ethically performed on a minor despite the minor's objection if the intervention is strongly in his or her best interests (e.g. necessary to save his or her life), this would be inappropriate in the case of experimental or non-standard interventions due to the poor evidence base.

7. The care team should give assurances that even if they are unable to provide interventions with poor evidence bases, the patient will continue to receive the best care that the hospital is able to provide (subject to any constraints arising from overload of hospital capacity).

Key terminology
(listed alphabetically)

Experimental/innovative intervention	Completely novel or significantly modified standard intervention with an insufficient level of evidence of safety or efficacy to introduce into routine care for the treatment of COVID-19, provided with the primary aim of benefiting a specific, pre-identified patient as part of their individual clinical care.[5]
Intervention	Any drug, device or procedure intended to result in an diagnostic, therapeutic or preventive outcome.
IRB-approved study	An activity that falls within the definition of research and has been approved by an Institutional Review Board (IRB) as set out in the Human Biomedical Research Act; Health Products Act; Health Products (Clinical Trials) Regulations; Medicines Act; Medicines (Clinical Trials) Regulations.
Nonstandard intervention/not generally accepted	An intervention that may not be new or novel but for which there is no generally accepted clinical application or professional consensus for COVID-19 treatment.
Product	Medicinal or therapeutic drugs, biologics and devices that fall within the regulatory scope of the HSA.
Research	Any systematic investigation initiated with the intention of developing or contributing to generalisable knowledge.
Standard care/intervention	An intervention that is generally accepted by the profession based on a balance of the best available evidence and according to best practice standards for the patient's condition.[6]

Acronyms
(listed alphabetically)

CEC	Clinical Ethics Committee as defined in the Healthcare Services Act
IRB	Institutional Review Board
HSA	Health Sciences Authority
SMC	Singapore Medical Council
SMC ECEG	Singapore Medical Council Ethical Code and Ethical Guidelines

[5] Adapted from Mastroleo, I, & Holzer, F. (2019). New Non-Validated Practice: An Enhanced Definition of Innovative Practice for Medicine. Law, Innovation and Technology Preprint, and in Singapore Medical Council (2016). Ethical Code and Ethical Guidelines. Available at: https://www.healthprofessionals.gov.sg/docs/librariesprovider2/guidelines/2016-smc-ethical-code-and-ethical-guidelines---(13sep16).pdf.

[6] Adapted from the SMC Handbook on Medical Ethics (2016). Available at: https://www.healthprofessionals.gov.sg/docs/librariesprovider2/default-document-library/2016-smc-handbook-on-medical-ethics---(13sep16).pdf.

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