DRAFT: Key criteria for the ethical acceptability of controlled human infection studies during public health emergencies

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WHO Working Group[1]

1. Preamble

Public health emergencies due to infectious diseases can be a major threat to global health and wellbeing. Research is a key part of emergency preparedness and response. Even with enhanced preparedness, the world will continue to face major epidemics and pandemics from novel or re-emerging pathogens. Research into such pathogens will therefore often take place during emergencies when there is a heightened public interest in the scientific and ethical aspects of research, and when it may be particularly challenging to strike an appropriate balance between competing ethical considerations. For example, there will often be large potential benefits of studies that can improve knowledge of the pathogen associated with an emergency, assist the development of vaccines and therapeutics, and/or inform appropriate uses of other control measures. Yet research on novel pathogens may also be associated with significant risks and/or uncertainties related both to the pathogen and any experimental vaccines or therapeutics being studied.

Controlled human infection studies (CHIS[2]) involve the deliberate infection of healthy volunteers. Such studies can be used to study infectious diseases in highly controlled settings. Such research can provide robust data about an infectious disease that would be difficult to obtain in other study designs, such as the precise understanding of when symptoms start after infection. Once a safe and reliable model of controlled human infection has been developed, studies can be conducted to evaluate interventions, including vaccines. However, CHIS are ethically sensitive for several reasons. First, such studies involve deliberately exposing participants to infection, unlike other types of studies that explore infectious diseases as they occur "naturally" in human populations. Second, assessing the social value of CHIS may be complex, especially during public health emergencies, requiring careful evaluation of practical, scientific, legal, and moral considerations. Third, proposals for CHIS with certain pathogens, including during emergencies, may raise questions about acceptable limits to risk and/or uncertainties in research. Fourth, like some other trial designs, CHIS may involve third party risks from onward spread of infection from participants. Fifth, participants have a right to withdraw from research, and respecting this right for CHIS participants may sometimes conflict with responsibilities to minimise risks to participants and third parties.

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[2] Also known as CHIM (controlled human infection models).

There are many ways that CHIS could be useful during a public health emergency. Public health responses to epidemic emergencies are enhanced by accurate diagnostic tests; safe, effective vaccines and treatments; reliable measures of correlates of immune protection; and improved scientific knowledge of the disease and its transmission. There are often large numbers of candidate vaccines and therapeutics, and well-designed CHIS may provide one of the most efficient and scientifically powerful means for testing and comparing them – especially where there are a large number of candidates, and/or where field trials are infeasible (e.g., due to low incidence of the disease in communities where field trials would be conducted). CHIS could thus be associated with substantial public health benefits in emergencies if they (i) accelerate or improve the development of vaccines and therapeutics, (ii) validate tests for infection or immunity, or (iii) provide other types of scientific knowledge relevant to public health responses.

Compared with alternative study designs, CHIS may be particularly well-suited to provide data on, for example, early or asymptomatic infection, the accuracy of diagnostic testing methods, immune correlates of protection, and the comparative efficacy of vaccine candidates in response to infection with a standardised viral dose. Such data can be more difficult to obtain with accuracy in alternative study designs, e.g. phase 3 vaccine field trials, which are typically less well-controlled than CHIS. In community studies, the exact timing of exposure to infection is typically unknown, the incidence of infection can be difficult to predict, individuals may be exposed to different viral strains and doses, multiple exposures are difficult to exclude, and asymptomatic infection may be difficult to detect. Consequently, assessing the effect of preventive interventions requires substantially larger sample sizes in community studies than in CHIS, and community studies must run for a longer duration for the number of individuals exposed to infection to accumulate. However, CHIS may sometimes be a slower method of testing vaccine efficacy compared to field trials, because developing a challenge strain and safe and reliable CHI model for use in subsequent studies may take several or many months. Standard field trials may produce more rapid results during high incidence epidemics. Further, the results of both CHIS and field trials regarding vaccine efficacy may become less relevant over time if, for example, the pathogen is rapidly evolving and/or initial trials are conducted with non-immune individuals but most people in the community develop immunity (from infection and/or vaccination) over time.

CHIS might be particularly likely to accelerate the availability of vaccines or therapeutics where there is appropriate coordination between researchers, manufacturers, and government agencies, including regulators. In any case, where CHIS are conducted, they should generally be integrated into wider research programmes involving larger studies to provide more precise estimates of safety and efficacy (e.g., phase 3 or 4 field trials and post-marketing surveillance of adverse events)(1). Larger field trials typically enable enrolment of more diverse populations of participants e.g., people with significant health conditions, pregnant women, and children. CHIS may nevertheless add value to other types of vaccine research by enabling (i) more accurate assessments of asymptomatic infection, (ii) potentially more rapid and standardized testing of vaccine candidates, and (iii) testing of vaccines in contexts where there is low natural transmission of a pathogen (for example, due to public health measures or during inter-

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epidemic periods) (2-4).[3] It is therefore likely that CHIS may have the potential to inform responses to future health emergencies.

Public trust in research and vaccines may depend on there being heightened vigilance to ensure that CHIS, if they proceed during an emergency, are conducted to the highest scientific and ethical standards(5). This document provides ethical criteria for the conduct of CHIS during a public health emergency with the pathogen that is the cause of the emergency[4]. The criteria are intended to be "pathogen agnostic", i.e., to apply to any such pathogen. These criteria have been adapted from those developed for COVID-19 CHIS(6) and are informed by other relevant WHO publications (7, 8). The following sections outline general considerations regarding the ethics of CHIS, ethical issues related to infectious disease research in emergencies, potential rationales for CHIS, and past experiences with this type of research during public health emergencies.

1.1 Ethics of human challenge or controlled human infection studies

Challenge studies have a long history, including early research with smallpox, yellow fever and malaria that changed the course of global public health(3) – although such studies were often less controlled than modern CHIS. In the last 50 years, CHIS have been performed safely in tens of thousands of consenting adult volunteers under the oversight of research ethics committees (3, 9, 10). These studies have recently helped, for example, to accelerate the development of vaccines against typhoid(11) and cholera(12), and to determine correlates of immune protection against influenza(13).

Research involving the deliberate infection of healthy volunteers may seem intuitively unethical, and there are numerous prominent historical examples of unethical research involving deliberate infection of research subjects(3). However, there is a consensus among ethicists who have reflected upon human CHIS that the intentional infection of research participants can be ethically acceptable under certain conditions (3, 7, 9, 10, 14-16).

CHIS are nonetheless ethically sensitive and must be carefully designed and conducted in order to ensure that relevant risks are minimised and that the rights and interests of participants are respected and protected.[5] Investigators must adhere to standard research ethics requirements and local research regulations. Furthermore, research should be conducted to especially high ethical and scientific standards where (i) studies involve exposing healthy participants to relatively high risks; (ii) studies involve first-in-human interventions (including challenge)

[3] Determination of experimental vaccine efficacy requires that a sufficient number of research subjects in both vaccinated and control arms are actually exposed to – that is, "challenged" by – the pathogen in question. To the extent that transmission is low, vaccine field trials may take more time and require larger numbers of participants to produce clear results than CHIS. In CHIS, by comparison, all participants are exposed, which is a major reason why they involve smaller numbers of participants and can be completed quickly.

[4] This document is therefore not intended to address specific ethical features of CHIS in preparedness for emergencies or in responses to perennial epidemic or endemic diseases.

[5] Among other requirements highlighted in this document, preserving public trust in research requires minimizing harm not only to volunteers but also to research staff and third parties.

and/or high levels of uncertainty (for example, about infection, disease and sequelae) [6]; or (iii) public trust in research is particularly crucial, such as during public health emergencies (2, 5, 16). Rigorous ethical standards for research might involve not only improvements in the design and conduct of the CHIS itself, but also, for example, appropriate accompanying community engagement activities(7).

Participants in CHIS typically receive payment, which is intended to reflect fair compensation for the time, effort, and expenses that volunteers commit to such studies(17). Since CHIS often involve large commitments (e.g., multiple days of inpatient isolation), significant payment is widely considered to be ethically acceptable, including in public health emergencies (3, 7, 17). As in non-emergency settings, protocols for CHIS should include justification for payment, and care should be taken to avoid a level of payment that may unduly influence participation. Payment for participation is separate from arrangements for financial compensation for any harms related to research, which, as for other clinical trials, is typically covered by appropriate study insurance(3).

The following sections first address research ethics considerations in public health emergencies, then review the role of CHIS in recent emergencies, and finally summarise possible ethically acceptable uses of CHIS during future epidemics.

1.2 Research ethics considerations in public health emergencies

Standard research ethics requirements continue to apply during emergencies. However, public health emergencies are unique and often very challenging contexts in which to design, conduct, and review infectious disease research, including CHIS. Compared to non-emergency infectious disease research, research on a pathogen that is the cause of an ongoing epidemic emergency may be characterised by (i) higher levels of uncertainty (especially regarding novel pathogens or variants), (ii) higher rates of community transmission of the infection, (iii) larger potential public health benefits (insofar as research results can be used to reduce significant disease burdens and/or optimise public health responses), (iv) increased research funding and activity, (v) potential high demands for medical care leading to shortages of healthcare resources, and (vi) higher levels of public interest and scrutiny, with increased potential that controversies regarding research may undermine public trust in science.

These features of epidemic emergency contexts may result in specific ethical issues becoming highly salient and in especially complex ethical tensions and/or trade-offs. For example, large potential public health benefits and high levels of public interest can lead to high perceived urgency of conducting research on the pathogen in general and CHIS in particular – and create a perceived need to expedite study planning and ethical review. Yet uncertainties about risks to volunteers and third parties, and high levels of public scrutiny can make research including CHIS more ethically sensitive in emergency settings, and review processes may need to be

[6] First-in-human CHIS may nevertheless involve less uncertainty than, for example, first-in-human drug trials because, for pathogens that have infected large numbers of people, human data regarding potential outcomes are already available.

especially rigorous and transparent(18). Further, high rates of community transmission may ~~not only place strain on healthcare personnel but also~~ mean that certain research questions (e.g., regarding vaccine efficacy) can be more rapidly and reliably answered in standard trial designs than in CHIS. Finally, although there may be substantial benefits arising from co-ordinated emergency research programmes, it may be challenging to co-ordinate and ethically evaluate multiple simultaneous programmes (potentially including CHIS), especially where the emergency is rapidly evolving and therefore data regarding risks and potential benefits of studies are also evolving.

The criteria provided in this document aim to inform decisions about the design and conduct of such studies by highlighting ethically salient features of CHIS research during epidemic emergencies. Rather than aiming to resolve complex ethical tensions, it is expected that decision makers will evaluate specific proposed CHIS research programmes in light of these criteria, data about the pathogen and ongoing epidemics, as well as local policies and regulatory requirements. Since this document is intended to be pathogen agnostic, it is expected that the weight of ethical considerations for and/or against CHIS will vary given a wide range of potential pathogens and emergency epidemic scenarios.

1.3 Recent Developments in Emergency Research Ethics

Recent epidemics have been associated with innovations in research and ethics review practices. For example, research activity was greatly increased and often expedited during the COVID-19 pandemic, and there were significant successes in co-ordination, such as multi-centre adaptive platform trials(19, 20). The efficiency of research ethics review was often increased, although there remain challenges regarding the balance between the rigour and speed of review processes; and the efficiency of review may also vary widely in different national and global settings(21-23). In the context of CHIS, in addition to ethical review, there was also significant public engagement activity(24), and co-ordination with government agencies regarding proposed research (25).

However, there remain additional opportunities for improving upon the ethical oversight of research related to public health emergencies. For example, capacity building activities should include further improvements in mechanisms for the co-ordination of research, sharing of data, and the translation of results into changes in global public health practice. Other ethical considerations include improving the transparency and consistency of research and review practices, and the development of innovative models of research ethics review aiming to combine speed and rigour. One proposed approach is to develop pre-approved "core" protocols for emergency research in interepidemic periods that could be updated and subject to final review at the time of an outbreak. Such models could be used for epidemic research in general, and CHIS in particular, but standardised norms for the use of pre-approved "core" protocols are yet to be developed or widely implemented (26).

Some public health emergencies have resulted in research ethics debates regarding specific issues that were in some respects difficult to predict in advance(27). Examples include issues related to congenital complications of infection in pregnant women during the Zika public health emergency(2, 28), and issues related to the long-term consequences of infection during the COVID-19 pandemic(29). On the one hand, these issues are not unique in that they can be

considered examples of third-party risk and risks or uncertainties for infected individuals, respectively. On the other hand, some issues which are highly salient to research in specific epidemics also touch on wider controversies or unresolved debates in research ethics. For example, there is not currently consensus in the research ethics literature regarding (i) the acceptability of third party risks(30) or (ii) appropriate risk mitigation measures for potential long-term hazards among participants(3). In many cases, it is impossible to eliminate such risks, e.g. because biosafety measures may fail even in the most optimal isolation facility or because exposure to infections or experimental pharmaceutical products likely carries a small risk of unforeseen harmful long-term outcomes. Each study therefore needs to be evaluated from an ethical perspective regarding such considerations, among many others. The intention of these criteria is thus to highlight relevant areas for additional consideration that may be highly salient during future epidemics, noting that the specific features of epidemics or study designs may vary.

1.4. Potential rationales for CHIS during public health emergencies

CHIS provide highly controlled study designs that can be used to:

(i) Study processes of infection, infectiousness, and immunity,
(ii) Measure the accuracy of tests for infection (e.g., PCR and antigen tests), and
(iii) Estimate the efficacy of interventions (e.g., vaccines and therapeutics).

Each of these types of uses can potentially address numerous scientific questions, many of which can also be addressed in different ways with alternative study designs. When deciding whether to conduct CHIS in an emergency it is important to consider such alternatives as well as the likelihood that CHIS and other types of research on the pathogen may occur in parallel and be mutually informative. Relevant non-CHIS research designs might include, e.g., observational studies of infection, immunity, and diagnostic strategies; and/or standard randomized controlled trials of experimental interventions (e.g. phase 3 vaccine field trials). The results of different types of studies may be more or less relevant, generalisable, or likely to inform changes to policy (e.g., regarding authorisation of pharmaceutical interventions or use of non-pharmaceutical public health measures) and must be evaluated on their merits, keeping in mind that their risks must be justified by the potential benefits.

Other practical considerations may also be relevant to ethical evaluations. For example, the time taken to set up a CHIS program may be ethically relevant for certain aims such as vaccine testing. Standard vaccine field trials can produce results regarding vaccine efficacy within a few months if commenced during a high incidence epidemic, whereas laboratory development of a challenge strain for CHIS may take several months. However, where community incidence is low, standard vaccine field trials may be slower and/or less feasible (e.g. because larger numbers of participants, potentially in more geographic locations, may need to be enrolled). Further, it is conceivable that CHIS could be conducted using methods of simulated "natural exposure" where participants who have been infected in the community are used as the source of infection for other participants, which could produce more rapid results than CHIS requiring laboratory development of a challenge strain(31).

To determine whether CHIS would be ethically acceptable during an epidemic emergency, decision makers must consider whether the scientific rationale and the expected public health benefits of such studies outweigh relevant risks and uncertainties relative to alternative study designs. Decisions should be informed by quantification of relevant considerations where feasible, e.g., regarding risks to participants (see Criterion 2). However, some considerations will be difficult to quantify, different study designs may be difficult to compare, and decisions will often involve weighing ethical considerations that are not commensurable. Moreover, different features of pathogens and epidemics may be relevant not only to estimates of the risks and benefits of CHIS but also to the comparison between CHIS and alternative study designs. To help illustrate these points, examples of previous experiences with CHIS during public health emergencies are summarised below.

4.1 Experience with controlled human infection studies in public health emergencies

COVID-19 CHIS

CHIS were proposed early in the COVID-19 pandemic to study SARS-CoV-2 infections(5). Although several research groups were already experienced with CHIS for infections with some similarities to SAR-CoV-2 (e.g., influenza), study protocols and ethical guidance suitable for use of CHIS during a pandemic had not yet been developed. Members of this Working Group developed Key Ethical Criteria for COVID-19 CHIS(6), which informed the design and review of first-in-human COVID-19 CHIS conducted in the United Kingdom(32). Such studies prompted significant scientific and ethical debate(24, 29, 31, 33-37). COVID-19 CHIS were also considered in other countries (e.g., United States and the Netherlands) but did not proceed. Details of what guided these decisions have not been made public as of 2023. Areas of controversy included (i) risks and uncertainties for volunteers, (ii) lack of specific curative treatment, and (ii) the extent to which such studies would accelerate vaccine development, especially after first generation COVID-19 vaccines proved efficacious (in standard "field" trials) in late 2020, within in a year of the pandemic being declared. In particular, the case for COVID-19 CHIS for initial vaccine efficacy testing became weaker over time, although this was not the only potential scientific rationale for such studies(38).

Initial CHIS for COVID-19 began in the UK in early 2021 with healthy young adult volunteers who had never been infected with, or vaccinated against, COVID-19(37-40), with further studies ongoing, including recruitment of volunteers with previous natural infection or vaccination. Although no new COVID-19 vaccines have been formally tested in CHIS to date, such studies could be used to test second or subsequent generation vaccines(41).

The primary benefits of COVID-19 CHIS to date have been (i) improved knowledge of the natural history and pathogenesis of infection, e.g., demonstration that volunteers often began shedding infectious virus from as early as 1 day after inoculation indicating the potential for very early transmission to others (which has implications for public health policy)(39); (ii) improved knowledge of immunity, e.g., refining correlates of protection(42); and (iii) data on viral testing methods(39). Regarding (iii), while polymerase chain reaction (PCR) was the main testing method used early in the pandemic, PCR is slow and expensive compared to antigen

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testing, e.g. lateral flow tests (LFT) / rapid antigen tests (RAT), and PCR tests remain positive often for many days after people are no longer infectious(39). COVID-19 CHIS confirmed that positive antigen tests were accurate for diagnosis, especially with serial testing. These studies also provided definitive data indicating that a negative antigen test was strongly correlated with volunteers producing no infectious virus. These data supported more widespread use of antigen testing, initially in the UK, which enabled rapid low-cost self-diagnosis, early access to treatments, reduced duration of isolation (with a negative antigen test enabling early clearance), and therefore reduced psychosocial and economic harms related to prolonged isolation (25). Despite concerns about potential risks to volunteers, COVID-19 CHIS caused no serious harms to participants (e.g., hospitalisations for COVID-19). However, as with natural infections, some volunteers did experience anosmia (loss of smell) for up to 6 months after challenge(43) – highlighting the need to consider long-term follow-up. Although initial protocols involved the use of antiviral medications, the use of such treatments was discontinued as participants had at most mild illness.

More generally, COVID-19 CHIS were an example of successful collaboration between academic researchers, government agencies, and private partners. Other examples include large multi-centre trials of COVID-19 therapies and vaccines(19). Such collaborations and their ability to facilitate high quality research were widely regarded as a major success of the response to the COVID-19 pandemic. However there remain additional opportunities to develop effective mechanisms for such collaborations, including regarding CHIS, in preparation for future public health emergencies(21, 44). However, COVID-19 CHIS remained controversial, including among research ethicists. Areas of controversy included uncertainties regarding potential long-term consequences of infection, the lack of highly effective curative treatments, and the social value of CHIS conducted after multiple vaccines were already authorised for use(29, 45). Among other things, this highlights the potential for reasonable disagreement regarding such studies and the potential for ethical considerations to change over time. For example, as the COVID-19 pandemic continued over several years, uncertainties regarding infection were reduced by accumulation of scientific data and the relative risks related to participation were reduced, but the benefits of testing vaccines in CHIS were also reduced by high rates of population immunity (due to vaccination and/or infection).

Zika CHIS

CHIS were also considered in the United States during the 2016-17 Zika virus disease emergency(2). An independent ethics report on Zika CHIS recommended against Zika CHIS during the emergency(2). The primary grounds for this recommendation were (i) uncertainty about the added value of Zika CHIS given the anticipated feasibility of standard field trials for testing vaccine efficacy (since such trials can rapidly provide estimates of efficacy during a high-incidence epidemic such as during the Zika emergency), and (ii) risks of transmission to third parties (especially male to female sexual transmission which could lead to congenital Zika syndrome)(2). However, Zika CHIS were later authorised in the United States once (i) field trials were no longer feasible as the incidence of Zika virus infection rapidly declined in 2017 (due to herd immunity in Latin America following high rates of infection), and (ii) greater

knowledge was obtained about the length of time participants would be infectious, resulting in identification of ways to substantially reduce risks to third parties (4, 46).

Challenge studies during historical emergencies

Challenge studies were also used during the 1918 influenza pandemic, illustrating that the use of such studies in emergencies has been considered for over a century(47). One difference is that, unlike the pathogens discussed above, 1918 H1N1 influenza was associated with substantial risks to young healthy adults. Further, such studies could not be subject to the same level of control as modern CHIS, in part because there were no reliable tests for influenza virus infection or for immunity to influenza. For example, "natural exposure" studies that attempted to infect participants via exposure to infected individuals failed to produce evidence of infection, and this may have been because volunteers who were exposed in these studies developed asymptomatic infection and/or already had immunity from prior infection(43).

Summary

CHIS are a unique type of infectious disease research that require careful scientific design and rigorous ethical evaluation. Given that such studies have been proposed and/or conducted during public health emergencies, and given that future epidemics or pandemics are inevitable, it is likely that CHIS will be proposed during future infectious disease emergencies. This document aims to provide guidance to scientists, research ethics committees, funders, policymakers, and regulators in deliberations regarding the use of CHIS in public health emergencies by outlining key criteria that would need to be satisfied in order for such studies to be ethically acceptable. Table 1 presents a summary of the criteria and parties who may be considered responsible for each criterion, while Table 2 summarises ethical considerations relevant to each criterion. The criteria in this document are intended to supplement, rather than replace, existing research ethics guidance and regulation and processes of research ethics review.

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2. Ethical criteria

The following list of criteria for the ethical acceptability of CHIS during emergencies is not exhaustive, and other research ethics standards and local requirements should be met (Table 1). This document has been informed by academic literature and frameworks for the ethics of CHIS (2, 16, 48). The criteria are not mutually exclusive: they are interconnected in numerous important ways. For CHIS to proceed during an emergency, it should be demonstrated that all seven criteria have been satisfied.

Criterion 1: Scientific justification

CHIS must have especially compelling scientific justification during public health emergencies

There may be several types of scientific justifications for conducting CHIS during health emergencies, with associated potential public health benefits of varying probabilities and magnitudes (see Criterion 2). Scientific justification would be strongest where studies aim to produce results of public health importance, especially to the extent that similar results could not feasibly be obtained as efficiently, rapidly, and/or rigorously in other study designs.

The justification for CHIS should situate them in a coherent overall strategy involving the coordination of research and other activities that ultimately aim to improve public health responses to the emergency (see Criteria 2, 3 and 4)(49, 50). The justification of CHIS should therefore include specification of their role in broader research programmes, including vaccine development pathways, and in the planning of public health responses (2, 49, 50).

Particularly important results would include those that would be expected to lead to large public health benefits or to benefits being achieved sooner than would otherwise be possible. This could occur, for example, where studies (i) inform the selection of the most promising vaccines (or treatments) from among multiple candidates for further study; (ii) test vaccines (or treatment) more efficiently than other study designs (e.g., when low community incidence of infection would be associated with longer duration or infeasibility of field trials); and/or (iii) inform other important clinical and public health measures (e.g., by generating knowledge regarding the accuracy of different diagnostic testing modalities, time between exposure and infectiousness, correlates of immune protection, or asymptomatic infection and transmission). Potential public health benefits are greatest where there is a clear plan of the pathways by which relevant knowledge, tests, vaccines or other interventions would be made widely available to decision-makers and those at risk.

Evaluations of the scientific justification for CHIS should include consideration of other study designs that explore similar scientific questions. For example, both CHIS and phase 3 field trials can be used to estimate the efficacy of vaccines. Potential advantages for CHIS as compared to vaccine field trials include (i) rapid generation of results regardless of community incidence of infection (whereas field trials will be slow to measure vaccine efficacy when community incidence is low), (ii) smaller sample size (e.g., meaning that fewer participants are exposed to any risks associated with experimental vaccines), (iii) increased potential to detect

early or asymptomatic post-vaccination infections. Potential disadvantages of CHIS compared to vaccine field trials include (i) the time taken to develop a laboratory strain for standard CHIS designs (which may delay vaccine efficacy testing and related public health benefits) and (ii) more stringent exclusion criteria (e.g., field trials may recruit people at relatively high risk of disease following infection, such as the elderly or immunocompromised, who would be excluded from CHIS).

Different CHIS designs may have different scientific justifications (as well as different risks and benefits – see Criterion 2). For example, while standard CHIS designs require time to develop a laboratory strain, it may be feasible to initiate simulated "natural exposure" studies more quickly, with a strain or variant of the pathogen that is currently circulating, which may enable the generation of timely and relevant results(31). However, there is less control of the viral dose and timing of infection in natural exposure studies as compared to CHIS where the experimental infection is developed in a laboratory and participants are directly inoculated by investigators; as a result, outcomes among exposed participants, including whether they become infected at all, may be more variable.

Investigators should aim to increase the scientific knowledge obtained while not undermining the primary aims of the study or exposing participants to undue risk (see Criterion 2). This could include, for example, collecting and storing additional samples during CHIS for subsequent analyses of host–pathogen interactions, testing accuracy(39), or risks of transmission(40). As an example of increased scientific knowledge obtained with zero or minimal risks to participants, COVID-19 CHIS involved the collection of environmental samples from participants rooms for viral testing(40).

Criterion 2: Assessment of risks and potential benefits

The potential benefits of CHIS must outweigh risks

- There should be systematic assessment of potential benefits and risks
- To the extent possible, these potential benefits and risks should be identified and quantified
- Potential benefits and risks should be compared with those related to alternative study designs
- Potential benefits should be maximised where this would not cause undue risk
- Risks should be minimized
- Risks and benefits should be evaluated to ensure potential benefits outweigh risks

It is a standard research ethics requirement that, on balance, potential benefits should outweigh risks(51, 52). Given the ethically sensitive nature of CHIS during emergencies, assessment of

their potential benefits and risks should be especially rigorous.[7] Potential benefits and risks should be evaluated for each of three key groups: (i) participants; (ii) society (in general); and (iii) third parties (e.g., those who might be infected by participants, including research personnel) (Table 2).

To the extent possible, the potential benefits and risks of CHIS should be identified based on available evidence (and, if necessary, modelled) and compared with those of other relevant study designs. To ensure that quantification, to the extent possible, is accurate and relevant, it should include data from large numbers of community cases of infection and be updated with the latest evidence if there are significant delays between the design and conduct of a CHIS. *Quantification of potential benefits* should include estimates of the extent to which data from CHIS could realistically be expected to inform policy regarding (i) the development or use of vaccines or therapeutics; or (ii) other public health measures (for example, how improved knowledge of the infectious period or different diagnostic testing strategies would inform quarantine and isolation policy).

The time taken to develop a laboratory strain may be relevant to evaluation of the benefits of CHIS during emergencies. For example, development of a laboratory strain may result in a delay to initiation of CHIS. During this time, initial vaccines may have already been tested in phase 3 field trials, which may reduce the benefits of CHIS if these first-generation vaccines are shown to be highly effective. Further, some pathogens may evolve into new variants over time. Pathogen mutation does not necessarily undermine the scientific rationale for conducting CHIS (nor other types of research such as vaccine field trials). Such mutation may limit some potential public health benefits (e.g., with respect to vaccine efficacy against more novel variants than those used to develop the laboratory strain) but not others (e.g., accuracy of diagnostic testing). However, CHIS may provide a unique opportunity to compare the features of infection with different variants in a controlled environment, which can be difficult to study in community settings where a pathogen is rapidly evolving.

Identification of risks should consider the probability, magnitude, and duration of potential harms (i.e., risks). It should also be acknowledged that there will often be uncertainty surrounding estimates regarding novel pathogens, and that unanticipated harms may also occur. However, uncertainty will decrease as a public health emergency continues over time and other research efforts clarify relevant features of a pathogen and the associated disease states. Further, some aspects of study design and associated risks (or benefits) will be known with reasonable certainty, such as the number of participants that researchers intend to infect during a CHIS (i.e., the attack rate) and the number who will be administered experimental interventions (e.g., vaccines).

Quantification efforts should therefore include estimates of (i) the number of participants exposed to risk (noting that CHIS involve exposing fewer participants to experimental interventions than standard phase 3 trials); (ii) absolute risk to participants, including any

[7] Similar considerations arguably apply in other situations of higher risk, greater uncertainty, and significant potential benefits (for example, some first-in-human drug or vaccine trials).

potential long-term harms (in light of the latest data); and (iii) marginal risk to participants (that is, the additional risk of participation compared to background risk of infection)[8]. (3, 53).

Marginal risk assessments should include consideration of features of the epidemic disease during a public health emergency and specific risks related to participation. First, such assessments should consider community infection rates, i.e., the chance of being infected outside the study (as compared to during the study), although short-term risk of infection may be difficult to evaluate if there are rapid changes in infection incidence during an epidemic. Second, the marginal risk of CHIS participation is also influenced by assessments of whether vaccines are likely to offer significant and lasting protection against disease. This is because participating in a challenge study early in an epidemic prior to the availability of vaccines may preclude participants from the benefit of being vaccinated before their first infection; this benefit is highest when symptomatic post-vaccination infections are rare or when vaccination would substantially protect those likely to enrol against risks of serious harm from infection. However, where symptomatic post-vaccination infections are (expected to be) common, as for most respiratory viruses (54), marginal risks of participation will be smaller. Further, where post-vaccination infections and re-infections are common, participants will likely be re-infected in the community after participation in CHIS. Among other things, this means that it may be difficult to determine whether any long-term adverse effects of infection are due to the experimental infection during the study or to subsequent community infections. Third, marginal risks may be higher if there is a potential risk of vaccine-enhanced disease from experimental vaccines(55).

Above and beyond the systematic assessment of potential benefits and risks, and the judgement of relevant decision-makers that the former outweighs the latter, expected benefits should be maximized and risks should be minimized, other things being equal. For example, if equivalent information can be gained using a research method or trial design that exposes participants to less risk, the lower-risk option should be adopted.

Table 2: Examples of potential benefits, risks, and risk minimization strategies (by group)

Group	Potential benefits	Risks	Risk minimization strategies
Society	Number of lives saved or decreased harm from earlier availability of a (safer or more effective) vaccine or treatment. Earlier return to normal social functioning and associated economic and public health benefits (due to results informing control measures)	Community spread of infection Erosion of trust in CHIS, research in general, or vaccines because of perceptions of CHIS in this context or harms that arise for participants or third parties	Infection control measures Public engagement regarding research design

[8] Marginal risk of participation may be very low during some public health emergencies where prospective participants are highly likely to be infected in the community. Participants in a CHIS may also receive especially timely and/or appropriate medical care during participation, which further reduces marginal risk.

Group	Potential benefits	Risks	Risk minimization strategies
Participants	Immunity induced by experimental vaccines (if effective) (in the vaccinated group, but not in the control group)	Risks related to experimental vaccines (including the potential for vaccine-enhanced disease) Risks of inpatient isolation (e.g. mental health)	Selection of participants at low risk of serious disease if infected. Recruit only as many participants as required to meet study objectives. Initial challenges conducted sequentially in groups of small numbers of participants, starting with low viral dose Close monitoring, early diagnosis and supportive care, including critical care if required Specific effective treatments (if they exist) Careful challenge strain selection Testing of vaccines with lower likelihood of causing vaccine-enhanced disease (e.g., based on prior animal studies) Long-term follow-up Compensation for any study-related harms
Third parties	Indirect benefits of participants becoming immune[b]	Risk of infection of research staff Risk of transmission of infection to third parties in the community Risk of congenital infection due to transmission from pregnant women to children	Selection of sites with stringent infection control processes, including protective equipment for staff Selection of participants to reduce third-party risks

b. Participants who become immune due to challenge infection (or an experimental vaccine) may be less likely to require healthcare for the disease and/or be a source of transmission in the community after completion of the study.

Risk management and minimization

The design of initial CHIS, if such studies proceed, should involve a range of risk minimization strategies (see Table 2). Third-party risks should be minimized by the use of protective equipment for trial staff and, if appropriate, the conduct of studies on an inpatient basis (until participants are no longer infectious) in facilities that permit stringent infection control.

Risks to participants should be carefully controlled and minimized. For example, participants in initial studies should first be challenged one by one or in small sequential groups, starting with a low dose of the challenge agent. There should be meticulous titration of viral dose, especially if there is an expectation of a positive correlation between viral dose and disease severity. A key risk minimization strategy should involve limiting participation to adult

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volunteers who are estimated, based on the best available data, to be at lowest risk, which will often be young healthy adults (see Criterion 6). This should involve the use of validated risk prediction tools based on data from community infections during the emergency(56), and revision of participant selection criteria in accordance with evolving evidence. Despite efforts to minimize risks, severe harms may still occur, for example if a participant has a risk factor for severe disease that has not previously been identified. There are thus strong reasons to conduct such studies especially carefully and to provide participants with guaranteed high-quality supportive care (including intensive care if required) during the study, long-term care and/or follow-up (for any lasting harms) after participation, and full compensation for any harms that occur that are attributable to participation in the CHIS. Such compensation may include provision of healthcare and is separate from payment for participation.

Investigators should revise challenge study designs with further risk minimization strategies, including provision of specific, curative treatment or use of attenuated challenge strains if or when these become available. Although treatment is one important way of reducing risk, the existence of specific, efficacious treatments is not a necessary condition for the ethical acceptability of CHIS(57).[9] However, if or when proven specific treatments are developed, these should be administered to participants if doing so is expected to reduce risks to a significant degree. This will involve consideration of who should be treated and at what time. Under certain conditions there may be a scientific rationale to delay or forego treatment (e.g., in order to collect additional data) but this must be weighed carefully against any additional risks to participants that would result.

The use of wild-type challenge strains may be ethically permissible, although challenge strains (whether wild-type or attenuated) should be as well characterized as possible in order to increase potential benefits and minimize risks. If an attenuated challenge strain that would be expected to produce results generalizable to wild-type infection is developed by the time studies are ready to commence, this would permit further minimization of risks. Although initial studies may involve non-immune individuals who have never been infected, CHIS involving previously infected and/or vaccinated individuals could also aim to determine correlates of protection and generate additional knowledge regarding immunity, risk of infection or re-infection following previous infection and/or vaccination.

Criterion 3: Co-ordination, consultation and engagement

Challenge research programmes should be co-ordinated with other emergency research and involve engagement with the public as well as appropriate consultation

Co-ordination

[9] For example, CHIS are approved and performed for pathogens with no specific treatment (for example, rhinovirus, rotavirus and dengue) as well as for influenza (for which existing antivirals may not always prevent complications of disease). Supportive care is provided in all cases.

CHIS research programmes should involve close coordination between researchers, funders, government agencies, and appropriate private sector partners**.** Ideally, mechanisms for co-ordination during epidemics should be prepared in advance of a public health emergency, especially given the significant groundwork required for CHIS and the advantages of timely results from studies initiated early in an emergency. Coordination activities during emergencies should situate CHIS within a coherent set of international or national programmes of research and aim to ensure that the potential public health benefits of relevant research can be realized with maximum safety and efficiency(50). Research should thus be coordinated with health agencies in order to (i) facilitate translation of results into public health benefits and (ii) avoid unduly compromising the local public health response to the public health emergency, for example during peak transmission periods(50). Studies should have adequate oversight from other relevant authorities (including WHO if appropriate).

All CHIS must be pre-registered in appropriate repositories, and during emergencies there should be a comprehensive list of all such studies maintained at the international level. Study data should be rapidly reported and ideally made publicly available (with appropriate protections). Especially important data include those regarding measures of vaccine or therapeutic safety and efficacy, those that would inform current public health measures (e.g., testing or isolation policies), and evidence of any significant harm to participants. It is expected that CHIS may be considered and/or conducted by multiple research groups during a major emergency, potentially in multiple countries, including potentially in low- and middle-income countries (LMICs) with existing capacity for CHIS. These programmes should, as far as appropriate, be co-ordinated, e.g. by being (i) standardized (in order to maximize benefits by obtaining comparable results in larger numbers of participants), and (ii) designed so as to avoid unnecessary duplication.

There should be coordination between researchers, policy makers and regulators regarding vaccine development. Early coordination with regulators should focus in particular on mechanisms for timely reporting and plans for how data from CHIS would be used (e.g., in the context of decisions to initiate field trials with promising vaccine candidates, and what role, if any, challenge study data would have in decisions regarding pre-approval, licensure, or emergency use of experimental vaccines)(2). Coordination is thus especially important where multiple vaccines are to be tested, as results from CHIS may facilitate the selection of more effective candidates by providing directly comparable estimates of vaccine efficacy that would otherwise be difficult to obtain. More generally, existing guidance frameworks for clinical trials continue to apply since there are few regulatory pathways specific to CHIS, however regulators may be more closely involved with CHIS during public health emergencies, especially where such studies aim to develop drugs and vaccines for novel pathogens (58).

Consultation

While recognizing the challenges of communication in an emergency setting, there should be simultaneous local and international consultation between researchers, ethics committee members, relevant experts in the science and ethics of CHIS, government agencies, and relevant private sector representatives. Such consultation should ideally help to ensure that the other criteria in this document are satisfied and that research designs are optimized, taking into

account collective expert views and input from public engagement. As part of consultation with relevant experts, challenge study designs should be the subject of independent scientific review (see Criterion 6). Consultation with local policymakers (for example within departments of health and other relevant government agencies) should aim to coordinate any proposed research with local public health policy and the pandemic response. Consultation and engagement (see below) should ideally be rapid, rigorous, and mutually informative, such that the views of the public and expert groups are updated in light of each other.

Public engagement

Programmes of CHIS research often involve public engagement(59-62). There is a stronger ethical case for such engagement activities during emergencies and, more generally, where CHIS involve novel pathogens or models of infection, novel volunteer populations, and/or higher levels of risk or uncertainty(7). Researchers and funders with an interest in the potential for CHIS during public health emergencies should therefore ideally consider the development of engagement programmes as a key part of emergency preparedness. At the outset of a public health emergency, engagement activities should ideally (re-)commence as soon as CHIS are being considered, and should continue throughout the research programme. Such activities may aim to, for example, explore community acceptance of CHIS, raise awareness about a (proposed) CHIS research program, and/or seek feedback on relevant aspects of study design (7, 24, 63, 64). There should be a focus on transparently presenting relevant risks and potential benefits (see Criterion 2) and, where appropriate, revising aspects of study design in light of the views of prospective, current, or previous challenge study participants (24, 61-65). It is expected that timely and well-designed engagement would not unduly delay potentially beneficial research and may in some cases improve enrolment.

There are now numerous examples of engagement activities related to CHIS(61, 62, 65), including during emergencies(24). Goals of public engagement might include assessing local acceptability of CHIS, responding to community concerns, maximizing transparency, and understanding the potential impact of research on the community (especially in light of other social and public health disruptions related to the emergency)(66). Engagement with (prospective) participants should additionally respond to suggestions regarding the conduct of research where appropriate, e.g., if this would reduce the risks or burdens related to CHIS participation. Methods should be appropriate to the specific context and could include online engagement techniques conducted by groups with relevant expertise. To maximize the benefits of these activities, they should be regularly updated in light of emerging data and ideally involve experienced social scientists working within the overall research programme and public health response(61, 65).

Criterion 4: Site selection

CHIS should be situated where the research can be conducted to the highest scientific, clinical, and ethical standards

Given the urgency, risk, and uncertainty involved, *initial* CHIS during a public health emergency should only be conducted in centres with significant experience in designing,

reviewing, conducting, and monitoring CHIS. These centres should also have access to appropriate facilities in which to prepare challenge strains with guidance from relevant local regulators. There should also be access to facilities able to ensure appropriate infection control measures and comfortable accommodation of participants. While the CHIS centres with significant experience are predominantly in high-income countries, there has been a recent increase in LMIC research centres with experience in conducting CHIS. Centres should also ideally have experience with community engagement (see Criterion 3). There should be provision for high-quality care (including intensive care if required), clear plans regarding long-term follow-up of participants, and full compensation for any research-related harm (see Table 2 and Criterion 2).

Background risk of infection is an important consideration in site selection. On the one hand, when local background probability of infection is high (e.g., during or soon before the peak of an epidemic in the local community), participants face less short-term marginal risk from being infected during study participation.[10] In pandemics (as opposed to geographically limited epidemics), the long-term expectation is that most people will be infected in the longer term(67). Nevertheless, the absolute risk participants face within a study remains an important ethical consideration, and care should be taken to minimize absolute risks of participation even where marginal risks are low (because background probability of infection is high) (see Criteria 2 and 5). On the other hand, peak periods of local transmission might be inappropriate times to conduct CHIS if such research would divert scarce resources (staff, protective equipment, health care) away from (other) public health response activities that should be prioritized during such periods(68).

Decision-makers will thus need to balance competing considerations, for example reduction of marginal risk for participants versus the coordination of research with the public health responses(50). It might therefore be appropriate, in some cases, to conduct CHIS where background risks are low, so long as the absolute risk to participants remains acceptable in light of relevant assessments (see Criterion 2), especially if conducting such studies in high-incidence settings is infeasible or would undermine the local public health response. Moreover, the scientific rationale for CHIS might often be stronger in interepidemic periods (when transmission is low) given that standard phase 3 vaccine field trials require significant community transmission and therefore must be very large or take more time to measure vaccine efficacy in low transmission periods(2, 69).

Criterion 5: Participant selection

CHIS should involve participant selection criteria that limit and minimize risk

[10] Background risk is a function of the probability of infection and the magnitude of harm related to infection or disease. Here, the key consideration is the background probability of infection. Higher background probability of infection reduces the marginal probability of infection accrued due to study participation (during which the proportion of participants infected may be very high). The magnitude of harm depends primarily on facts about the participant's risk of severe disease – and participants who face a higher expected magnitude of harm should be excluded, especially in initial studies (see Criteria 2 and 6).

The safety of participants is a core consideration for evaluating the ethical acceptability of CHIS. Participant selection criteria must be designed so that there is a high level of confidence that participation is as safe as possible. Initial studies should thus be limited to adults at the lowest risk of severe disease, which will often be young healthy adults. Within these groups, selection criteria should exclude individuals at higher risk of harm from infection (e.g, by screening to identify relevant undiagnosed health conditions) or higher risk of harm due to the burdens of study participation (e.g., those with significant mental health issues that would be likely to be exacerbated by isolation).

Data during epidemics may find that sub-populations with certain characteristics are at higher average risk of severe disease, such as those from ethnic groups that are socio-economically disadvantaged in specific societies. However, participant selection should aim to be as inclusive and representative of relevant populations as possible. Potential participants may be excluded based on individual risk, which may be associated with membership of a group (e.g., immunocompromised individuals), but should not be excluded on the basis of being a member of a specific sub-population that is perceived to be "vulnerable". Such approaches reflect changes in research ethics standards which previously supported the categoric exclusion of entire "vulnerable populations" from participation. It is now recognised that (i) individuals face different kinds and levels of vulnerability that do not necessarily track membership in a population group(70), and that (ii) exclusion of participants on this basis of group membership may result in limited generalisability of results if there are differences between relevant groups (e.g., regarding vaccine efficacy)(3).

Even with well-designed selection criteria that minimise risks, participants may still face absolute risks or levels of uncertainty related to infection with an emerging pathogen that might be high (although still within acceptable upper ranges of research risk) as compared to some other "non-therapeutic" studies with healthy volunteers. For example, CHIS with a novel pathogen during an emergency may involve more risk or uncertainty than many well established CHIS and some phase I drug trials (2, 3, 71-74). In addition to other risk minimization strategies, selection criteria should thus be updated promptly in light of emerging evidence that would help to stratify prospective participants further and thus enable selection of those at (even) lower risk of harm (see Criterion 2). If such data justify confidence or reasonable suspicion that any particular (sub)groups are at significantly heightened risk of serious illness (or death) resulting from infection, then they should be excluded from participation in initial studies.[11]

Selecting participants who are low risk (for severe disease following infection or adverse effects from experimental vaccines or other trial interventions) may involve prioritizing the

[11] Under certain conditions, it may be appropriate to include some groups at higher risk (such as older individuals) in later studies where this would be important to permit the development of interventions for these groups and where similarly useful data regarding higher-risk groups could not be obtained in a lower-risk study population (or other lower-risk study design). Similar approaches have been used in a challenge study for respiratory syncytial virus that has recently been safely conducted with older adults (who face higher risks than younger adults) after initial studies in younger adult participants (see https://clinicaltrials.gov/ct2/show/NCT03919591,).

safety of participants over the generalizability of some types of results to higher-risk participants (for example, older individuals and those with comorbidities; see Criterion 1). Prioritizing the safety of participants is standard in modern CHIS and acceptable if studies with low-risk participants nevertheless produce useful results (e.g., that would help to identify the most promising vaccine candidates, which may also be relevant for higher-risk individuals)(3). Issues of generalizability are not unique to CHIS(75), and the results of CHIS, e.g., regarding vaccine efficacy, have often been generalizable to diverse populations that differ from those enrolled in CHIS(10, 11).

Criterion 6: Expert review

CHIS should be reviewed by an appropriately qualified independent committee

Initial CHIS during an emergency should be the subject of specialized independent review in addition to or in conjunction with a standard local ethics review. Similar considerations may apply to other types of research that may be controversial or potentially involve higher levels of risk and uncertainty. In all cases, review procedures should incorporate substantial relevant expertise and be conducted in a timely manner (potentially in parallel) without compromising the stringency of review. There should be regular consultation between investigators and (at a minimum) the relevant ethics committee(s), including immediately before and during the conduct of the study, especially in light of emerging data (e.g. regarding risks).

A specialized review committee should include members with relevant scientific expertise and members with research ethics expertise specific to CHIS. Given the urgency of public health emergency contexts, committees with experience in conducting rigorous emergency review may be well placed to conduct (local or independent) review. In order to improve pandemic preparedness, greater capacity should be built and maintained to permit such review in more locations in future(21).

Even where a local or institutional ethics committee has relevant specialized expertise, there should be independent review of *initial* CHIS during an emergency, as such studies may be particularly controversial and their conduct may have implications beyond the local setting (e.g., regarding coordination of research efforts, or global public trust in research; see Criterion 3). Independent review should ideally be conducted at the national or international level (for example by WHO or an appropriate national agency). If initial CHIS produce no unexpected harms or public concerns specific to the research, it may be reasonable for subsequent CHIS (if any) with the pathogen to be reviewed according to usual practices in the relevant jurisdiction.

Criterion 7: Informed consent

Consent processes for CHIS must be rigorous and robust.

Informed consent processes should be particularly rigorous in CHIS during emergencies because of the heightened potential uncertainties involved(3, 76). Data-driven approaches to

consent can help ensure adequate understanding and appreciation of what participation in CHIS entails. For example, CHIS routinely incorporate tests of participant understanding during the informed consent process(3, 77). Such tests are also important in CHIS during emergencies. Tests of understanding should be based on the best available data regarding risks (and uncertainties) as well as relevant evidence regarding how important and complex information should be conveyed to participants to maximize understanding(24, 77).

Consent should be revisited throughout the study, as is often the case for other CHIS. This should occur, for example, when new relevant data (e.g., regarding risks) become available after the study has commenced, and immediately prior to challenge. Consent processes and participant selection criteria (see Criterion 5) should be designed with the goal that participants have capacity to make a decision, have relevant study information disclosed to them, comprehensively understand what participation entails (and the alternatives), give their voluntary agreement to participate, and are able to authorize their participation.

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Table 1: Key Criteria for the Ethical Acceptability of CHIS During Public Health Emergencies

	Criterion	Explanation	Responsible parties
1	Scientific justification	CHIS must have especially compelling scientific justification during public health emergencies	Research Team Ethics committee Funders & Sponsors Independent Oversight Committees
2	Assessment of risks and potential benefits	The potential benefits of CHIS must outweigh risks	Research Team Ethics Committee Independent Oversight Committees Regulators Funders & Sponsors
.3	Co-ordination, consultation, and engagement	CHIS research programmes should be co-ordinated with other emergency research and involve engagement with the public as well as appropriate consultation	Research Team Funders Government Agencies
4	Site selection	CHIS should be situated where the research can be conducted to the highest scientific, clinical, and ethical standards	Research Team Ethics Committee Funders Government Agencies
5	Participant selection	CHIS should involve especially careful participant selection to limit and minimize risk	Research Team Ethics Committee
6	Expert review	CHIS should be reviewed by an appropriately qualified independent committee	Ethics Committee Government Agencies Independent Oversight Committees
7	Informed consent	CHIS must involve rigorous informed consent	Research Team Ethics Committee

Research team: Investigators, local institution(s).

Independent oversight committees: data safety management board (DSMB), trial oversight committee, local safety monitors, etc.

Government agencies: Regulators, Departments/Ministries of Health and/or Public Health, etc.

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