Article:
Yu, M., Darton, T.C. and Kimmelman, J. (2020) Decision analysis approach to risk/benefit evaluation in the ethical review of controlled human infection studies. Bioethics, 34 (8). pp. 764-770. ISSN: 0269-9702

https://doi.org/10.1111/bioe.12773

A Decision Analysis Approach to Ethical Evaluation of Human infection Challenge Studies

Michael Yu, PhD[1], Thomas C. Darton, MRCP(UK)ID, DPhil[2], Jonathan Kimmelman, PhD[1]*

1. Biomedical Ethics Unit/Social Studies of Medicine, 3647 Peel Street, McGill University, Montreal, QC, Canada

2. Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield Medical School, Beech Hill Road, Sheffield, United Kingdom

* Corresponding Author. James McGill Professor in Biomedical Ethics Unit/Social Studies of Medicine, 3647 Peel Street, McGill University, Montreal, QC, Canada

Tel: (514) 398-3306, Email: jonathan.kimmelman@mcgill.ca

Word Count:

Acknowledgments:

Funding:

Interest Conflicts:

ABSTRACT:

Balancing the stakes of a human infection challenge study, where healthy volunteers are deliberately exposed to infectious agents to gain knowledge about diseases and potential vaccines, requires transparent, systematic, verifiable, and non-arbitrary ethical evaluations. Decision analysis promotes these qualities in ethical evaluations through four steps: (1) determining explicit criteria and metrics for evaluation, (2) identifying alternatives to the study, (3) defining the models used to estimate the metrics for each alternative, and (4) running the model to produce the estimates and compare the alternatives. In what follows, we describe how decision analysis might be applied by funders or others contemplating the conduct of infection challenge studies.

Human infection challenge studies (HICs) involve the deliberate exposure of healthy human adults to infectious agents. Researchers frequently use them to study the efficacy of candidate vaccines, which is achieved by vaccinating healthy volunteers with the candidate(s) prior to administration of the infection challenge. Outcomes from these studies, in particular, the proportion of volunteers developing clinical or laboratory signs of infection or disease, can then be used to support or reject further evaluation of the vaccine candidate(s) in phase III field trials or its redevelopment (1,2). On occasion data from HICs have also contributed directly to product licensure (3), an approach that might result in considerable cost-saving and acceleration in vaccine research and development.

Nonetheless, the use of HICs has been ethically contentious. Historic infection challenge studies, such as studies of Hepatitis A in Children at Willowbrook (4), or Walter Reed's Yellow Fever Studies, are centerpieces in many accounts of questionable human research practices (5). In contemporary settings, the deliberate infection of healthy volunteers has raised ethical questions about acceptable risk and burden of demarcated research procedures (6,7).

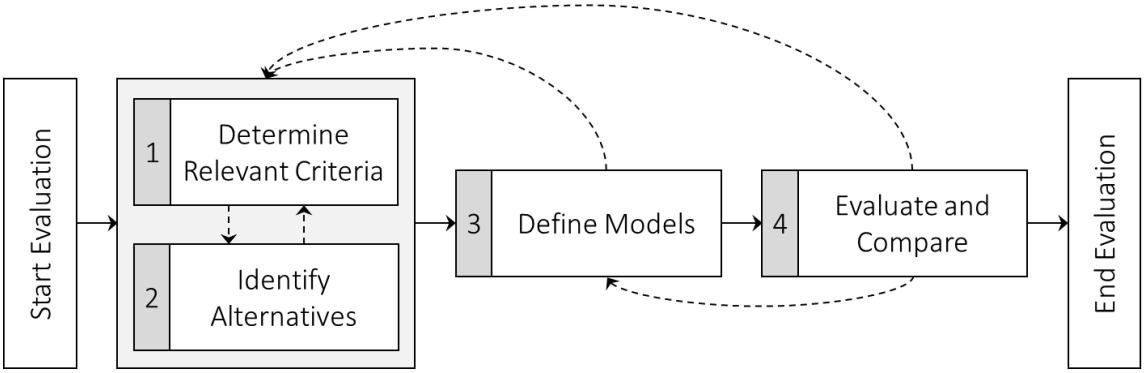
In this work we show how a decision-analysis approach might inform the moral evaluation of risk and benefit for proposed HIS studies for vaccine development. Decision analysis uses a formalized approach to recognize, manage, and resolve complexity. This is done through the development of explicit models that support transparency, systematicity, verifiability, and non-arbitrariness in making a decision. Decision analytic techniques have been used to inform health policy (8–10), clinical care (10–15), the setting of research priorities (16–18) and the analytical design of clinical studies (19,20).

Decision analysis can complement the ethical evaluation of contentious research proposals, like those involving HIC, in two ways. First, decision analysis produces a stronger basis of evidence for ethical evaluation of risk and benefit. By interrogating the inputs of an ethical evaluation and the goals of a study, and breaking down those components into smaller tasks, decision analysis can identify areas where more rigorous analytic tools are needed. This approach to decomposing a problem, considering smaller parts to a complex question before reintegrating them into the larger question, has been found to improve judgments in several domains (21–23). Second, decision analysis helps make the ethical principles of transparency, systematicity, verifiability, and non-arbitrariness espoused by the Belmont Report manifest in ethical evaluation. It promotes transparency by presenting explicit models, inputs, and assumptions, which allows different stakeholders to comment on different elements of a HIC evaluation. It promotes systematicity by following a formalized process, which helps the different components of a complex problem receive the attention they deserve and clarifies the limits of the conclusions that can be drawn. It promotes verifiability by encouraging the use of reliable sources of evidence, which can help recruit better knowledge for answering the problem. It promotes non-arbitrariness by defining the process in which a HIC evaluation may be resolved. This, in turn, can be applied with reasoned modifications to the evaluation of other HIC proposals and refined over time.

In the following, we will discuss the potential role of decision analysis for funders and institutional review boards, with the general idea that funders may be better equipped to produce and review the decision analysis, whereas institutional review boards may be more focused on its review. We will return to the practical implementation of decision analysis at the end.

The steps to decision analysis

Decision analysis consists of 4 key steps (Figure 1). The first is determining the criteria with which to evaluate a proposal. The second is identifying alternative approaches for achieving the same goals. The third step is modeling. Developing a model involves determining the right inputs needed to assess each criterion for each alternative and the right process required to combine them to form an estimate. The fourth step involves making the final sets of estimates and comparing each alternative based on the estimated values. In many cases, this last step may involve estimating criteria for the alternatives under different scenarios (e.g., worst-case, best-case and most-likely scenario), then deciding how each of the scenarios would inform the final decision. Each step can inform those preceding it, leading to iterative refinements in the evaluation. In what follows, we show how each task might be applied to evaluate HIC study proposals.



Step 1: Determining relevant criteria

A first set of criteria relates to the risks participants in a HIC might face, which includes the discomforts they may experience as a result of the deliberate exposure to the challenge agent and potential adverse events that may occur as a result of the study procedures. To evaluate these criteria, they need to be measurable and thus should be translated into a set of metrics ("units of measure"). We propose that metrics for risks be derived from the symptomology of the infection under investigation—considering their type, severity, and duration—which may have been used by earlier studies of the disease or infection, and any adverse events that have been linked to the study procedures or the candidate vaccines in prior studies. In this step, we define what metrics to use. We discuss *how* to estimate the values for these risk metrics in the section on defining models.

A second set of criteria relate to the "knowledge gain" that a HICs produces. The amount and variety of knowledge generated can differ substantially depending on the research question(s). In contrast to field trials (addressed more in the next section), the highly controlled nature of HICs has the potential to generate more detailed knowledge regarding disease pathophysiology and host immunobiology, in addition to providing a vital 'early' signal as to whether the vaccine candidate *could* work in the target (human) host. However, there are important limitations on the its signal of whether the candidate vaccine *would* work in its intended setting. For example, an HIC might recruit healthy adults from affluent US or European to test vaccines that are often intended for children in different geographic settings. HICs also often use biological agents that differ from the infectious agents causing the disease in the human target population (1,2). If different types of knowledge are valued, evaluators should consider separate metrics for each type. For knowledge gain, we propose a metric based on how much a HIC is expected to change the beliefs of an expert community of vaccine developers. Knowledge gain about whether a vaccine would be effective in the target setting, for example, can be measured using

the expected change in probability the experts would assign to the vaccine having a clinical benefit in the field before reviewing the results of an HIC and after. Research is pursued to change beliefs around hypotheses. Studies that are expected to change belief to a greater degree, all else being equal, should have greater value. We discuss how to estimate this metric in more detail in the section on defining models.

The set of criteria considered define the scope of the evaluation. For an institutional review board, the evaluation may focus on the criteria noted above—risks to participants and potential knowledge gain. For funders, the evaluation may start with the same concerns but add in questions around public trust, the cost of the research, and the time required to complete the research. In making these criteria transparent, the review process invites stakeholders to comment on whether the ethical evaluation is comprehensive. Translating the criteria into metrics may further narrow the effective scope of the evaluation. When it is not possible to select a metric that fully describes a criterion, the limitations of the metric should be noted and can be used to supplement interpretation of that metric when needed. Nonetheless, by developing well-defined metrics, evaluators will also have a common language with which to discuss the criteria, reducing ambiguity when these criteria begin to be evaluated and compared and removing arbitrariness in interpretation.

Step 2: Identify alternatives

While a proposed HIC could may produce useful knowledge regarding the potential field efficacy of a new vaccine, it is not the only way to generate that knowledge. Other approaches might be able to satisfy the criteria more fully—generating better knowledge gain or perhaps sacrificing some knowledge gain for lower risks. There are three main alternatives to consider: a modification of the HIC study design, a different research method altogether, or forgoing the research entirely.

Modifications to the design of a HIC can influence how well an HIC attains the different criteria specified in the decision analytic model. Metrics for participant burden, for example, can be reduced by excluding specific participants who might be particularly sensitive to an infection, as was done with blood group O participants from a cholera challenge study (24). HICs might also use laboratory biomarkers to predict the ensuing onset of infection, allowing early treatment and the attenuation of symptoms (25). Study designs might be further modified, for example, by use of historical control groups. Such changes are not without their tradeoffs. In each of the examples provided, this reduction in participant risk can introduce noise in the findings or can distance the experimental setting from the field, leading to a potential loss of knowledge gain.

Different research methods might include (further) animal or non-human primate studies or advancing directly into field trials. These alternatives differ in their ability to meet different criteria of the model. Compared to a HICs, field trials produce knowledge that may more relevant to the populations for which a vaccine is intended and thus more easily translated into policy recommendations. Evaluators with a broader scope might consider additional criteria, such as the years to complete a field trial compared to the months that might be expected from a HIC. HICs, as a method to accelerate vaccine research and development, potentially enables swifter actions to be taken in infectious disease outbreaks and epidemics. The metrics used to assess risk might also need to be modified to capture the differences between exposing a relatively small number of challenge study participants versus inactive, passive collection of natural exposure data in a much larger population, as might occur in a vaccine field trial.

A final option is to consider not conducting the research at all. In some cases, the choice not to continue may be evident from the initial evaluation, with risks too severe to justify the potential knowledge gain. However, evaluators should also consider the value of a HIC in the light of ongoing developments in scientific, clinical and ethical research. When the state of knowledge is rapidly changing, the potential knowledge gained from the study could be quickly outdated and its value depreciated.

Step 3: Defining the models

The first two steps, determining criteria and identifying alternatives, can be compared to steps in the design of a clinical trial—determining the endpoints and comparators. The next step, defining a model, can be compared to developing a clinical trial's protocol and analysis plan. A decision analytic model specifies how data will be collected and combined to estimate the different metrics. Each metric may be estimated using a different process, even for the same metric across different alternatives. More important metrics often demand more precise and sophisticated methods of estimation, whereas less important metrics may be evaluated more simply. The model will also be shaped by the resources (e.g., data and analytic tools) available to evaluate each metric.

Some metrics may be relatively straightforward to estimate. As noted earlier, several metrics for patient burdens may be determined by previous studies into the disease. The same studies can also provide the initial estimates for what participants are expected to experience—with meta-analyses or systematic reviews providing more robust values. Still, evaluators might not use these estimates directly. If the study population or the challenge agent vary from those in the literature, the estimates may need to be adjusted to account for these differences.

Other metrics, such as expected knowledge gain, may require more sophisticated approaches. The proposed metric for expected knowledge gain is the expected change in probability an expert community would assign to a candidate vaccine being effective in the target setting before viewing the results of a HIC and after. Bayesian methods can be used to estimate this change in probability, requiring as an input (1) an initial estimate of the probability that the candidate vaccine is viable (a "prior"), (2) an initial estimate of confounding variables, and (3) information on the statistical properties of the study design. The first two inputs may be estimated using data from previous studies on this vaccine, of similar vaccine candidates, or elicited directly from a sample of experts when neither of those sources are available. The latter input can be assessed from the statistical design of the study itself. For both the risks and expected knowledge gain, the final estimates can then be traced back to verifiable sources.

Step 4: Evaluate the models and compare alternatives

The remaining step is to run the model—collecting data, calculating estimates for the metrics, and comparing the identified alternatives based on these metrics. The first set of models run will often be based on the 'best' estimates that can be generated from the data. In some cases, these best estimates may be reasonably reliable, for example, if the data are collected from a large systematic review and meta-analysis. In other cases, the best estimates may be founded on shaky inputs. If, for example, the data comes from a limited sample of animal studies, evaluators might doubt the rigor not only of those findings but of the estimates based on them.

Having followed the previous steps, evaluators nonetheless have a powerful tool to handle such uncertainty, running the model using a range of different inputs. Running the models with alternate inputs allows evaluators to identify what inputs are important to get right. If small changes to certain inputs lead to large changes in the final estimates for the metrics, evaluators should attempt to find more precise estimates for those inputs. For any uncertainty that cannot be reduced, evaluators should then consider a range of the possible outcomes. Representative scenarios, such as those based on the most likely, reasonable best-case, and reasonable worst-case scenarios, can be used as guideposts for those evaluations.

The final product of this process is a systematic, transparent, verifiable evaluation of the different alternatives under consideration and a robust foundation for discussing the correct approach. This information can help guide ethical discussions by bringing clarity to various uncertainties.

A Worked Example of How Decision Analysis Can Inform Ethical Evaluation

Imagine a research team undertaking an investigation aimed at supporting the eventual licensure of a candidate vaccine for preventing the spread of an infectious disease. Understanding of the disease pathology is advanced, but the researchers have an additional hypothesis that disease severity may be higher given the presence of a specific biomarker. While the researchers are predominantly interested in advancing the candidate vaccine towards licensure, information about their biomarker hypothesis could be useful in understanding how best to administer the vaccine or to design future studies. Thus, in step 1, the researchers work with policy-makers and ethicists to define their metrics. First they define two knowledge gain metrics—the expected change in belief that the vaccine is safe and effective, and the expected change in belief for the biomarker hypothesis. Second, they define risk and burden associated with testing as another criterion.

In step 2, the research team identifies four plausible research methods for achieving their objectives of advancing a vaccine candidate towards licensure. The first is conducting further animal studies of the vaccine. Several animal studies of the vaccine, include studies in non-human primates, suggest that the vaccine shows significant promise. While some additional knowledge could be gained from animal studies, differences in biology makes such knowledge gain limited. In particular, the biomarker of interest is only present in humans and thus cannot be evaluated in an animal study.

A second research method is an HIC, which could produce greater knowledge about both the vaccine's efficacy and the biomarker hypothesis but involves risks to participants who otherwise would not have been exposed to the disease. Returning iteratively to step 1, the research team focuses on three types of burden as markers of welfare loss: discomfort as a result of exposure (measured by the percent of participants expected to experience a temperature above 39.5 ˚C for over 36 hours); the risk of hospitalization as a result of adverse events (a severe allergic reaction) from the vaccine administration (measured by the percent of participants expected to be hospitalized), and the number of participants who will be needed for the study; the planned HIC would require 100 participants.

Concerns about the discomfort have led the investigators to consider a third method, an alternative HIC design in which participants with the biomarker are excluded. Under this design, fewer participants are expected to experience severe discomfort, but the knowledge that can be gained about the biomarker hypothesis becomes much more limited. Knowledge gain about licensure also is more limited, as

lessening the overall symptom severity may hinder the assessment of the candidate vaccine's disease modifying potential.

The research team is considering a fourth way of achieving their research objectives: moving straight into a field trial. Knowledge gain on efficacy and safety is expected to be greater, since the candidate vaccine will be used in the setting in which it is intended. However, field trials have significantly less control and thus results are expected to be noisier—limiting some of this potential gain. Given these considerations, knowledge gain regarding the biomarker hypothesis should be superior to the HIC with the biomarker exclusion, but lower than what would be learned from a better-controlled HIC with no biomarker exclusion. As a field trial, no participants will be deliberately exposed to the infectious agent, so no additional discomfort is expected as a result of the study procedures. However, the administration of the vaccine could still lead to adverse events and thus hospitalizations. To detect efficacy for the vaccine, the estimated number of participants that will be required is 15000.

Finally, the research team also considers what might happen if no research is conducted. The candidate vaccine the researchers are studying are one of several that are currently being investigated. While many of these other candidates have yielded mixed results, two show significant promise. One is nearing completion of its first HIC and, if effective, is likely to be accelerated into field testing. Another vaccine has only completed two animal studies, but the results of those studies initially suggest a surprising degree of efficacy. The progress of those vaccines

After a series of deliberations, the researchers in step 3 agree to a model for evaluating each metric for each alternative. For the animal study, HIC designs, and field trials, inputs are sought through systematic reviews and/or consulting a sample of experts for values to feed into the model. The systematic reviews were summarized using meta-analysis and a statistical model was developed to estimate expected knowledge gain, with the aid of the members of the research team who developed the statistical analysis plan for the HICs. For the alternative where no research is conducted, the researchers initially assume that this should lead to no knowledge gain or risks (associated with their own study procedures). However, a member of the research team notes that some knowledge gain on the biomarker hypothesis might still be realized, based on the results of the candidate vaccine currently completing its first HIC. Another member notes that, while the other studies will not produce any knowledge about the safety and efficacy of the specific candidate vaccine this research team is studying, gaining that knowledge is less pressing if a safe and effective candidate vaccine can make it to the market first or if a vaccine with a better safety and efficacy profile is discovered. After further discussions on whether to revise their criteria to capture some of these dimensions (going back to step 1), the research team decides that estimating these metrics are—for the time being—beyond their scope of evaluation. However, the research team will note these considerations and evaluate the other alternatives in light of them. If the later discussions (in step 4) become contentious, then the team may revisit adding and estimating these new criteria.

In step 4, the researchers ran the model for each design, except the no research alternative, under three different scenarios: a reasonable worst-case, a most-likely case, and a reasonable best-case scenario. Table 1 represents the hypothetical output of the decision analysis performed.

	Non-human primate study			HIC No biomarker exclusion			HIC Biomarker exclusion			Field trial		
	Worst-Case	**Most Likely**	**Best-Case**	**Worst-Case**	**Most Likely**	**Best-Case**	**Worst-Case**	**Most Likely**	**Best-Case**	**Worst-Case**	**Most-Likely**	**Best-Case**
Knowledge gain												
Biomarker hypothesis[1]	0%	0%	0%	0%	20%	30%	0%	5%	10%	0%	15%	25%
Safety and Efficacy[1]	0%	2%	5%	0%	15%	25%	0%	12%	22%	5%	20%	30%
Discomfort caused by study procedures												
Temp > 39.5˚C for 36h[2]	0%	0%	0%	75%	45%	15%	65%	25%	10%	0%	0%	0%
Adverse events caused by study procedures												
Hospitalization[2]	0%	0%	0%	2%	0.1%	0.05%	0.2%	0.1%	0.05%	2%	0.1%	0.05%
Resources / participant burdens												
Participants[3]	0	0	0	100	100	100	100	100	100	2000	2000	15000

[1] Expected change in probability assigned to the hypothesis (biomarker, safety and efficacy of vaccine) by an expert community; increases and decreases in belief are weighted equally

[2] Expected percent of participants who will experience a condition as a result of the study procedures

[3] Expected number of (human) participants required

The output of the decision analysis can serve as the basis for an informed, ethical deliberation of the alternatives. In considering the alternatives, the research team quickly concludes that further animal studies do not appear justified. While (human) participant risks are effectively nonexistent, the knowledge gain is not large enough to be meaningful. Somewhat more debate surrounds the option to move forward with a field trial. A 30% expected belief change (as in the best-case scenario) would represent a meaningful shift in expert opinion. However, given the current state of knowledge, even if the belief change were favorable, it would be unlikely to be large enough to justify licensure outright. Follow-up studies would likely be required to further shore up belief. Given that, even under the best-case scenario, a follow-up study would be likely, the expected incremental knowledge gain of 5-8% relative to either HIC study does not appear to merit the increased participant burden. Moreover, during the discussion, a member of the research team notes that the nature of the participants are very different. Of particular concern is the reputation of the researchers with the target community. If the researchers conduct too many field trials in that population, it may erode the community's trust. This additional concern is noted on the evaluation.

In deciding between the two HIC designs, the debate becomes more contentious. Some members of the research team note that the design with no biomarker exclusion criteria generates much better knowledge on the biomarker hypothesis and slightly better knowledge on its safety and efficacy. Other members suggest that knowledge on safety and efficacy is of more practical importance and the slightly better knowledge may not justify the increased risk of severe discomfort. These latter members also remind the team that knowledge about the biomarker hypothesis may be gained even if they do not test it directly. Other research teams are completing studies that will inform that hypothesis. Finally, a few members highlight that, while the two designs have similar profiles regarding adverse events, the design with no biomarker exclusion criteria has a worse profile for adverse events under the reasonable worst-case scenario. These members cite arguments that in evaluating risks, the worst-case scenario should be given greater weight (26,27). Overall, the research team concludes that while both HIC designs have a favorable risk benefit ratio, members of the team disagree on which design best meets the criteria of ethical research.

Finally, the research team revisits their assessments of the alternatives considering what would happen if they do not conduct research. Members of the research team studying the candidate vaccine soon to complete its first HIC have communicated that early results have been disappointing and that their vaccine may not be as effective as initially believed. Members of the research team for the candidate vaccine in the early stages of animal testing remain confident about their vaccine—but note that several additional animal studies have been planned and will be needed before human trials. These communications lead the research team determines that the knowledge gain from an HIC is likely to remain valuable given its timeliness and the lack of potential alternatives.

Decision analysis provides a crucial foundation for a reasoned, ethical evaluation. Decision analysis does not tell evaluators whether risks are reasonable. It tells evaluators what those risks are, under different scenarios, and how much is expected to be gained by undertaking those risks. Decision analysis does not tell evaluators whether a certain amount of knowledge gain merits a certain increase in participant burden. However, it makes the nature of those tradeoffs clear and renders the choice between them explicit.

Implementation of Decision Analysis in Ethical Review

Decision analysis requires effort. Not all domains of clinical research may warrant such effort, but for those that are ethically contentious, such as HIC, the greater transparency, systematicity, and verifiability may demand it. Decision analysis encourages more considered choices in research that can better promote the welfare of patients and participants. Decision analysis also creates a record of past decisions that help evaluators learn and make better ones.

Funders, such as those with a heavy portfolio in infectious diseases, can benefit from a programmatic application of decision analysis. The skills to perform this analysis may need to be developed, but they do not need to be created from scratch. As noted, decision analysis is already used in medicine (16–20) and funders may be able to draw on this expertise. Funders might also require information from research teams, which may often be only a slightly different form of what they are asked to currently produce. For example, research teams already need to assess the discomforts participants are likely to face in a HIC, and funders may simply request that the research teams provide better clarity on the expected discomfort and uncertainty around it.

IRBs can then use the output of these decision analyses as an input into their deliberations. While IRBs may not need to perform the decision analysis, they too will need to develop some skill in teasing out the moral dimensions of decision analysis outputs. As with other parts of the IRB submission, they should be free to interrogate the researchers or the funders about the information provided to them. For example, there may be circumstances (e.g. a public health crisis) where basing decisions on the best-case scenario output is most appropriate; other circumstances (absent a crisis) where decisions might be informed by the more pessimistic outputs. We leave the moral interpretation of decision analysis outputs to future analysis. In using decision analysis, the IRB is better able to focus on the ethical components of the evaluation, while benefiting from the increased clarity about the risks, benefits, and outstanding uncertainties of the proposed study.

Conclusions

Human infection challenge studies can produce valuable knowledge on the efficacy of a vaccine in a timely manner, but, as they involve the deliberate infection of healthy volunteers, they can be ethically complex. Decision analytic approaches provide a way to resolve many of the complexities associated with evaluating the potential risks and knowledge gain associated with a HIC. The output of such an analysis can then inform the broader evaluation of the ethics of a particular HIC trial—augmenting the discussion with greater analytical rigor, promoting the better use of information, reducing ambiguities in meaning, and encouraging stronger justification. While this may require some additional effort, these steps can help us to better serve those that might benefit from the results of a HIC and those who might bear much of the burdens of such research.

References

1. Darton TC, Blohmke CJ, Moorthy VS, Altmann DM, Hayden FG, Clutterbuck EA, et al. Design, recruitment, and microbiological considerations in human challenge studies. Lancet Infect Dis. 2015 Jul;15(7):840–51.

2. Roestenberg M, Hoogerwerf M-A, Ferreira DM, Mordmüller B, Yazdanbakhsh M. Experimental infection of human volunteers. Lancet Infect Dis. 2018 Oct;18(10):e312–22.

3. Levine MM, Chen WH, Kaper JB, Lock M, Danzig L, Gurwith M. PaxVax CVD 103-HgR single-dose live oral cholera vaccine. Expert Rev Vaccines [Internet]. 2017 Mar 4;16(3):197–213. Available from: https://www.tandfonline.com/doi/full/10.1080/14760584.2017.1291348

4. Robinson WM, Unruh BT. The Hepatitis Experiments at the Willowbrook State School. In: Emanuel EJ, Grady C, Crouch RA, Lie RK, Miller FG, Wendler D, editors. The Oxford Textbook of Clinical Research Ethics. New York: Oxford University Press; 2008. p. 80–5.

5. Lederer SE. Walter Reed and the Yellow Fever Experiments. In: Emanuel EJ, Grady C, Crouch RA, Lie RK, Miller FG, Wendler D, editors. The Oxford Textbook of Clinical Research Ethics. New York: Oxford University Press; 2008. p. 9–17.

6. Baumgaertner E. Ethicists Call for More Scrutiny of “Human-Challenge” Trials. The New York Times. 2018 Apr 20;

7. Miller FG, Lyerly AD. Navigating Ethics Review of Human Infection Trials With Zika [Internet]. The Hastings Center; [cited 2019 Apr 1]. Available from: https://www.thehastingscenter.org/navigating-ethics-review-human-infection-trials-zika/

8. Dowie J. ‘Evidence-based’, ‘Cost-Effective’ and ‘Preference-Driven’ Medicine: Decision Analysis Based Medical Decision Making is the Pre-Requisite. J Health Serv Res Policy. 1996;1(2):104–13.

9. Elliott H, Popay J. How are policy makers using evidence? Models of research utilisation and local NHS policy making. J Epidemiol Community Heal. 2000;54:461–8.

10. Petitti DP. Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis: Methods for Quantitative Synthesis in Medicine. New York, NY: Oxford University Press; 2000.

11. Hunink MGM, Galsziou P, Siegal J, Weeks J, Pliskin J, Elstein A, et al. Decision making in health and medicine. Cambridge, UK: University Press, Cambridge; 2001.

12. Thornton JG, Lilford RJ, Johnson N. Decision analysis in medicine. BMJ Clin Res. 1992;304(6834):1099–103.

13. Lilford RJ, Pauker SG, Braunholtz DA, Chard J. Getting research findings into practice: Decision analysis and the implementation of research findings. BMJ. 1998;317(7155):405–9.

14. Zarin DA, Pauker SC. Decision analysis as a basis for medical decision making: The tree of hippocrates. J Med Philos (United Kingdom). 1984;9(2):181–214.

15. Pauker SG, Kassirer JP. Decision Analysis. New Engl J Med. 1987;316(5):250–8.

16. Claxton K, Posnett J. An economic approach to clinical trial design and research priority-setting. Health Econ. 1996;5(6):513–24.

17. Claxton K, Ginnely L, SchulpherM, Philips Z, Palmer S. A pilot study on the use of decision theory

and value of information analysis as part of the NHS Health Technology Assessment programme. Health Technol Assess (Rockv). 2004;8(31):1–103.

18. Soares M, Welton N, Harrison D, Peura P, Shankar-Hari M, Harvey SE, et al. An evaluation of the feasibility, cost and value of information of a multicentre randomised controlled trial of intravenous immunoglobulin for sepsis (severe sepsis and septic shock): incorporating a systematic review, meta-analysis and value of information analysis. Health Technol Assess (Rockv). 2012;16(7):1–186.

19. Ades AE, Lu G, Claxton K. Expected Value of Sample Information: Calculations in Medical Decision Modeling. Med Decis Mak. 2004;24(2):207–27.

20. Willan AR, Pinto EM. The value of information and optimal clinical trial design. Stat Med. 2005;24(12):1791–806.

21. Armstrong JS, Denniston WB, Gordon MM, Armstrong JS, Denniston WB, Gordon MM. The use of the decomposition principle in making judgments. Organ Behav Hum Perform. 1975;14(2):257–63.

22. Bonner SE, Libby R, Nelson MW. Using decision aids to improve auditors' conditional probability judgments. Account Rev. 1996;71(2):221–40.

23. Connolly T, Dean D. Decomposed versus holistic estimates of effort required for software writing tasks. Manage Sci. 1997;43(7):1029–45.

24. Cohen MB, Giannella RA, Losonsky GA, Lang DR, Parker S, Hawkins JA, et al. Validation and characterization of a human volunteer challenge model for cholera by using frozen bacteria of the new Vibrio cholerae epidemic serotype, O139. Infect Immun. 1999 Dec;67(12):6346–9.

25. Sheehy SH, Duncan CJ, Elias SC, Choudhary P, Biswas S, Halstead FD, et al. ChAd63-MVA–vectored Blood-stage Malaria Vaccines Targeting MSP1 and AMA1: Assessment of Efficacy Against Mosquito Bite Challenge in Humans. Mol Ther [Internet]. 2012 Dec;20(12):2355–68. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1525001616322389

26. Hare C. Risk and radical uncertainty in HIV research. J Med Ethics [Internet]. 2017 Feb;43(2):87–9. Available from: http://jme.bmj.com/lookup/doi/10.1136/medethics-2015-103117

27. Hey SP, Kimmelman J. The risk-escalation model: a principled design strategy for early-phase trials. Kennedy Inst Ethics J [Internet]. 2014 Jun;24(2):121–39. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25109092