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Public Health Ethics in Practice

A background paper on public health ethics for the UK Public Health Skills and Knowledge Framework

April 2017

This document has been produced on behalf of lead agencies across the UK including Public Health England, Public Health Wales, NHS Scotland and the Public Health Agency of Northern Ireland, in response to a need expressed by the public health workforce across the home nations. The document supports the Public Health Skills and Knowledge Framework (PHSKF) which is a UK-wide resource. A list of the steering group agencies who have supported work on the PHSKF is shown on p21.

The review of the PHSKF (including this paper) was commissioned by the Department of Health, and project managed by Public Health England.

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Published: April 2017
PHE publications gateway number: 2016566

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Acknowledgements

We would like to acknowledge and thank the trainees, practitioners and leaders within the fields of public health, public health ethics and public health law from England, Wales, Scotland, Northern Ireland and Canada who provided comments and advice on an earlier draft of this document.

In particular, we would like to thank Woody Caan, Claire Cotter, Vikki Entwistle, Anthony Kessel, Keith Syrett, Farhang Tahzib, Ross Upshur, Caroline Vass, Tom Walker, Jamie Blackshaw, Andrew Wood, Loretta Sollars and John Morris. The final document reflects the authors' views and we take full responsibility for its contents.

Contents

1. Introduction: Ethics as a central part of public health

The Good Public Health Practice Framework 2016, produced by the Faculty of Public Health and the UK Public Health Register, defines public health as "the science and art of promoting and protecting health and wellbeing, preventing ill-health and prolonging life through the organised efforts of society". In expanding on this definition, the document emphasises that:

- public health activity takes a population approach
- there is a shared responsibility for health across society
- this requires social co-ordination, with a key role for the government working in collaboration with other partners

The framework explains how public health activity is directed to the improvement of population health outcomes. This is an ethical mandate derived from a commitment to achieve greater good. It also says that public health agendas aim to address social inequalities in health and wellbeing. This is an ethical mandate derived from a commitment to social justice.

Given these ethical agendas, and a commitment to programmes of activity that look to the prevention of disease, promotion of wellbeing, and to ameliorating the social determinants of health, ethics clearly finds a central place in public health. The references to population approaches and social co-ordination, furthermore, imply a role for political morality in understanding the state's public health responsibilities to assure the conditions in which people can be healthy – and understanding which means are permissible to use in establishing these conditions.

In short, the question of when practitioners, public authorities, or other actors should (or should not) act to serve population health cannot be properly answered without reference to values and ethical arguments. Nor can we evaluate how legitimate a particular intervention is without understanding its ethical implications. As such, ethics should not be viewed as an afterthought to be examined once policy adoption or intervention selection has taken place; it is an integral component of public health decision-making that should be incorporated into all aspects of policy and practice.

While ethics is central to public health policy and practice, it should not be presumed that all moral values will be equally shared by every public health policy-maker or

practitioner. This is so for different reasons.[1] Policy development and implementation can make reference to different moral values from the values used by practitioners in their individual decision-making. Individuals and groups can reasonably disagree as to relevant values or their respective weighting. Public health policy-makers and practitioners also possess varying degrees of ethical understanding and levels of ethics education/training, which can lead them to reach different moral conclusions to the same question. All of these considerations must be kept in mind, and caution exercised, when developing ethics as a core competency. This is true too when considering how ethical frameworks for public health should be developed and used.

This part of the Public Health Skills and Knowledge Framework (PHSKF) therefore provides an introduction to public health ethics both as a philosophical field of inquiry and as an applied area that guides practice and policy. Ethics in various forms can be seen pervading throughout the PHSKF in its technical, context and delivery functions. It contains commitments to professional ethics, such as responsibility for leadership and working collaboratively; to substantive ethical concerns, such as improving health outcomes and reducing health inequalities; and to procedural ethical concerns, such as including individuals and communities in decisions that will affect their health and wellbeing.

An understanding of ethics should thus be considered a key competency for people working in public health. To underscore this competency, various areas of skill and knowledge must be addressed. At times, it requires the capacity to deliberate and evaluate ethical issues, ie to be able to identify and assess the ethical components of a public health problem and the ethical implications of responding to it in different ways. This capacity can be developed through independent study, ethics courses within degree programmes, and continuing professional development.

There are also ethical decision-making tools available to practitioners and policy-makers that can help in recognising and responding to ethical issues. Some of these tools are focused on providing ethical guidance to individuals, eg a statement of professional values that can be used as a deliberative aid in reasoning through what to do in different circumstances. Other tools are focused on providing ethical regulation to an entire group, eg regulation or policy on a specific issue that dictates how practitioners should specifically work their way through a morally-contentious issue. In addition to materials available from scholarly sources, various public health agencies around the world have been developing materials, such as case books, which provide useful resources that can be drawn on.[2]

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[1] See, for instance, Barry N Pakes, Ethical Analysis in Public Health Practice (PhD Thesis, University of Toronto, 2014); Maxwell J Smith, Public Health as Social Justice? A Qualitative Study of Public Health Policy-Makers' Perspectives (PhD Thesis, University of Toronto, 2016).

[2] See, for instance, Canadian Institutes of Health Research – Institute of Population and Public Health, Population and Public Health Ethics: Cases from Research, Policy, and Practice (Toronto: University of Toronto Joint Centre for Bioethics, 2012); CDC, Good Decision Making in Real Time: Public Health Ethics Training for

The overview of public health ethics in this document is a precursor to an inclusive, directed exercise that will lead to the development of a public health ethics framework and associated materials.

This document is organised as follows:

Section 2: explains public health ethics with reference to the longer-standing field of bioethics.

Section 3: indicates in greater depth the scope of public health ethics as a field of philosophical inquiry.

Section 4: explains the links between that field and public health ethics as a direct source of professional norms and standards.

Section 5: concludes with a list of references to useful materials.

Different points are made with reference to case study examples. The importance of ethics to good public health practice and policy cannot be overstated. As such, a grounding in public health ethics skills and knowledge is a crucial responsibility for practitioners, public health leaders, and policy-makers.

Local Health Departments (Atlanta: CDC, 2012); WHO, Ethics in Epidemics, Emergencies and Disasters: Research, Surveillance and Patient Care (Geneva: WHO, 2015); Drew H. Barrett, et al. (eds.), Public Health Ethics: Cases Spanning the Globe (Springer, 2016).

2. Public health ethics and bioethics

Public health ethics may be viewed as a part of bioethics. However, as this section demonstrates, public health ethics is widely, and with good reason, considered a field in its own right. Different histories of bioethics present contested accounts of when it emerged as a field, with what rationales, and with what purposes. Notwithstanding these conflicting accounts, it is possible to identify the second half of the twentieth century as a time when scholars from fields including philosophy, theology, law, sociology and medicine developed bioethics as a concerted area of study and practice.

In principle, and to a great extent in practice, bioethics focuses on any moral question concerning life, so embraces areas as diverse as environmental ethics, science ethics, and veterinary ethics, to name just three. Nevertheless, many commentators have observed that bioethics, whilst touching such areas, has had an overwhelmingly dominant concern with medical ethics. This dominance has arguably distorted ethical analysis and practice in fields outside of clinical medicine, including public health. As such, it is instructive to consider and contrast emphases that have been taken from the medical ethics literature, and explain why these are inappropriate for public health ethics.

As noted in the introduction, public health activity requires a focus on health at a population level, it looks to questions regarding overall and differential health outcomes across society, and works through effecting measures that prevent ill health and promote good health. As such, the ideas of ‘treatment’ and ‘the patient’ are often radically different in a public health context as compared with a clinical context. In the latter, the focus is generally on the immediate impact and implications of an intervention between a physician and a patient. Nevertheless, the dominance of norms from within medical ethics is so strong that they have impacted on how people approach public health ethics.

A variety of philosophical literatures exists in medical ethics, but particular values have come to predominate. This fact has arisen out of a concern that, historically, the practice of medicine gave insufficient account to the rights of the patient, favouring a paternalistic, ‘doctor knew best’, approach (intervening to serve a person’s wellbeing rather than focusing on informed consent). Such a view was compounded by a related concern that medicine was governed too much by professional self-regulation, with inadequate legal oversight and accountability. The most famous and influential position within medical ethics is the so-called ‘Georgetown mantra’, which presents the ‘four principles of biomedical ethics’: autonomy, non-maleficence (do no harm),

beneficence (do good), and justice.[3] Prominent works in bioethics seek to explain how ethical medical decision-making requires attention to these principles, and why the principle of individual patient autonomy should be considered the 'first among equals'.

Even within medical ethics, there are critics of the high value placed on autonomy in a clinical context. It is argued, for example, that we have moved from a situation in which patient autonomy was wrongly disregarded to a situation where it is wrongly treated as being of supreme importance. Critics of the dominance of patient autonomy paint a picture wherein individual choice wrongly counts for everything, where paternalism is considered always to be wrong, and wherein other important values are ignored. Furthermore, it is argued that this form of medical ethics fails (even with its reference to justice) to account for population-level concerns and approaches. The practical focus of mainstream medical ethics is distorted by a lens that is set to focus on individual clinical interventions.

Given that public health agendas address whole populations rather than just individuals, advocate for prevention more than treatment, and are concerned with values beyond autonomy, a mainstream medical ethics is not suitable as a basis for public health ethics.

It is important to understand the nature of the concern here. Within public health ethics there are advocates who favour a great premium being given to individual liberty or autonomy: libertarian theorists, and many political commentators opposed to the 'nanny state', for example, argue against health promotion campaigns or public funding of health systems as being illegitimately intrusive.

The fundamental problem regarding the reduction of public health ethics to medical ethics is that medical ethics, as generally conceived, is not apt in the first place to address public health problems. A starting-point of autonomy and individual consent disregards the fact that many population-level interventions cannot be governed according to medical norms that regulate, for example, processes to achieve informed consent. Public health measures incorporate general policies, focus on populations, and involve the co-ordinated and collective regulation of a wide range of actors (eg manufacturers, advertisers, local authorities).

Public health ethics must be developed in a way that is appropriate to the practical arena of public health. Reference to medical ethics is of (at best) limited utility. Rather, knowledge and understanding of public health ethics will only be achieved if we can account for:

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[3] Tom L. Beauchamp and James F. Childress, Principles of Biomedical Ethics, seventh edition (Oxford: Oxford University Press, 2012)

- what it means to take a population approach, including population-level ethical analysis
- the principle that responsibility for health is shared across society; it is not just a question for individuals considered in isolation
- the need, rather than focus on an individual, reactive intervention, to consider ethical methods of social co-ordination, which incorporate measures that target whole populations, often whose constituents are not (yet) unwell

The following two sections will explain these points in greater depth, first by considering how philosophical theory should be understood in relation to the above points, and then explaining how philosophical ethics connects to professional ethics. Prior to that, though, consider the following case study, which exemplifies why public health ethics cannot be addressed by a bioethical approach that is reduced to medical ethics.

Case study 1: Reducing childhood obesity

According to the WHO, 'childhood obesity is reaching alarming proportions… and poses an urgent and serious challenge'.[i] Levels of obesity are rising generally across the UK, and it is a phenomenon that is particularly prevalent among members of poorer, urban communities. While we might all agree that we should try to reduce levels of childhood obesity, particularly in disadvantaged groups, there are many different public health interventions that could be adopted in designing a multi-faceted campaign to achieve this outcome. We want to ensure the interventions we select can be ethically justifiable.

If our ethical framework were grounded in medical ethics, it might allow us to evaluate the appropriateness of implementing interventions aimed at individual children (eg one-to-one behaviour change or gastric band surgery). So long as we obtain parental consent and the intervention is in the child's best interests, for instance, we could justify undertaking such measures.

Most of the interventions we would want to undertake, however, will be aimed at all children who are, or are at risk of being, overweight and obese as a population. With a medical ethics framework focused on individual patients in the clinical setting, and the primacy of obtaining consent before we subject anyone to any intervention, we would find it very difficult ethically to justify interventions aimed at the population level. Anything from simply measuring, monitoring and reporting on levels of obesity (eg national child measurement programme) to public information and education campaigns (eg nutrient labelling systems, nutritional literacy courses within school curricula) to interventions that may end up targeting persons who may not have a problem with obesity (eg sugar tax, banning the use of trans-fats) involve a population focus that requires a different kind of ethical framework that can account for these relevant considerations. A medical ethics approach would also not be helpful in providing guidance as to how to obtain permission to run such interventions or whether opt out versus opt in arrangements are more appropriate.

In designing and selecting ethically appropriate interventions to reduce childhood obesity, standard frameworks from medical ethics do not provide what is needed. We need to make use of ethical frameworks that can incorporate population factors and social determinants of obesity, can account for all of the actors responsible for reducing obesity (eg government, industry, schools) and be able to evaluate the tools and approaches used by these actors to achieve the social co-ordination necessary to implement effective, population-wide interventions. It is only public health ethics frameworks that provide this, especially with their reliance on moral, political and legal theory as a basis to address these wider questions.

i World Health Organization, *Report of the Commission on Ending Childhood Obesity* (Geneva: WHO, 2016), p. vi

3. Public health ethics: moral and political theory

The previous section has explained why mainstream medical ethics is not well suited to questions in public health. To move more positively towards an applicable public health ethics, it is important to have an understanding about the value of theory and the implications of different sorts of theory. As well as this being important in itself – for example, to assist in deliberation on and evaluation of different ethical problems – it is theory that ultimately underpins more prescriptive professional ethical frameworks, such as those that are discussed in the next section. Consider, therefore, how public health ethics theory operates.

First, it should be understood that theories can have both explanatory and normative roles. It is through theories that we explain, for example, why a particular social group suffers health inequalities, and through theories that we analyse whether that group's unequal status is permissible, or whether there is an obligation to address it. The first sort of theory here is descriptive: it is empirically grounded and reports how the world is (eg scientifically robust epidemiological studies underpin the claims that are made about the health status of populations).

The second sort of theory is normative: it is philosophically grounded and reports how the world should be. The force of normative reasons is what supports the claims made. These normative theories may be evaluative (eg stating why health inequalities are bad or worse than some other status) or prescriptive (eg stating why we ought to take particular means to reduce or alleviate health inequalities).

Scientific evidence will tell us that a particular social group disproportionately suffers poor health outcomes. A normative theory will tell us why health inequalities are a question of justice, and whether and why we should act to respond to these inequalities as a moral problem – and not merely a technical problem of how to reduce gradients of inequality.

Questions of justice pervade much of public health policy and practice – and there are diverse normative theories that can be used to address questions in public health. Through engaging with normative theories – and ethical frameworks informed by them – we are able to make use of a specialist language that articulates key concepts and ideas for understanding ethical questions raised by public health. These theories also provide us with a basis for analysing the reasons, evidence and arguments in favour of, or against, undertaking potential public health interventions from an ethical perspective. Such theories, for instance, can provide an account of why health

inequalities are unfair, why this unfairness is also unjust and what we would be justified in doing to remedy such health inequalities.

The Faculty of Public Health expresses widely-held views about the problems of social inequalities in health: a guiding ethical concern in public health is to address such inequalities. However, agreeing on why and how inequalities are problematic raises many questions. Are we concerned with the equality of achievement of good health, or just equality of opportunity to achieve it? Are we concerned about equality of values other than health (for example, happiness, financial security, friendship), and if so how are they to be balanced against one another? How are we to identify particular social groups as deserving prioritisation? What resources is it acceptable to redistribute, and interventions to institute, in order to achieve better health equality?

In order to explore and answer complex questions such as these, it is necessary to understand that they fall within the realm of political philosophy. Political philosophy does not limit itself to the study of interpersonal ethics. Rather, it examines our obligations as citizens, explains how we may understand the obligations of institutions (including, for example, the royal colleges, industry actors, universities), and how we understand legitimate government power and its limitations.

Philosophical work in public health ethics, conceived as a study in political philosophy, allows theorists to explain what duties the state has, for example, to ensure food quality standards, to ensure that there is a sound public health infrastructure, or to respond to environmental hazards that arise. These wider questions of political morality are important to consider in how political and democratic processes impact on the delivery of health, social care and other services (cf. PHSKF Function B4)

Relevant political ideas here are philosophical rather than ‘party political’. They concern what we as socially-related and interdependent persons should do in structuring our lives and institutions in the regulation of our collective actions together. Case study 2 explains the fundamentality of political theory to public health ethics.

Case study 2: Fluoridation, political theory and public health agendas

Most agree that people have a right to access clean water. Whether fluoride should be added to public water supplies is, however, regarded by some as a controversial question, despite the consensus of scientific bodies around the world that it is an effective and safe public health measure. According to Public Health England, 'Dental caries (tooth decay) is a significant public health problem in England. Sizeable inequalities in the incidence of caries exist between affluent and deprived communities, and it is a common cause of hospital admissions in children.'[ii] Yet, despite this, some people oppose community water fluoridation as a public health intervention on ethical grounds.

Given the nature of the intervention, community water fluoridation reaches all people connected to the public water supply and will be implemented by government agencies using public funds. Those who do not want fluoridated water may find it inconvenient and costly to make alternative arrangements for their drinking water. Evasion would be costly and burdensome. There is a whole host of ethical questions to face in deciding whether it would be ethically appropriate to fluoridate the public water supply. Are we justified in overriding individual wishes for the common good? Should the fact that the people who would benefit most from this intervention suffer from higher levels of disadvantage and ill health create an extra claim in favour of fluoridation? Should interventions that affect whole populations be subject to public engagement exercises to be seen as legitimate? Does the likely difficulty for individuals to make alternative arrangements where they are opposed to the intervention make it unduly coercive or burdensome? Is this different to opposition to any other aspect of the public water supply such as the raw water composition or chemicals added to render it potable, such as chlorine or aluminum compounds? These are the kinds of questions that political theory engages with and has the theoretical resources to evaluate on which basis public health interventions can be justified.

Different ethical values will be raised in debates on fluoridation. Some will argue that individual autonomy is so important that the government has no right to fluoridate, regardless of any potential benefits. Others will argue that solidarity and fairness require that such a programme is necessary to protect vulnerable groups. Others still will disagree on the relative weights of the benefits and harms, or on the standards/level of evidence necessary before a decision should be made. Recourse to normative theories can provide public health practitioners and policy makers with a robust way to evaluate and adjudicate different arguments in relation to the justifiability of community water fluoridation and allow for the provision of coherent and consistent conclusions.

ii Public Health England, *Water Fluoridation: Health Monitoring Report for England 2014* (London: PHE, 2014), p. 4

4. Public health ethics: professional ethics

We have seen how ethical questions are intrinsic to public health, and how public health ethics must draw from political philosophy rather than medical ethics. For public health policies and interventions to be ethically justified, they must be defensible by reference to political theory. For a sound public health ethics, an underpinning political theory will explain the basic justification for (or for not) making a particular intervention. This can be, for example, a theory of political liberalism, against which problems, such as those outlined in case studies 1 and 2, may be evaluated.

However, it is clearly not always possible for practitioners to examine public health questions in philosophical depth. Just as it is appropriate for evidence bases to be condensed and decision-making tools developed, so it can be desirable for ethics frameworks and models to be created to assist public health policy-making, deliberation and activity.[4] Such frameworks will serve in addition to general concerns of professional ethics (eg through commitment to values such as openness, honesty, and transparency). Decision-making tools focused specifically on public health problems must be based on robust theory, as per the discussion in the previous section. But they will provide a simplified means for their users to engage in public health ethics without direct engagement in theory.

Ethical frameworks can aid deliberation in various ways. They may serve to increase ethical awareness, for example, by exposing previously implicit ethical dimensions. They may provide direct guidance, for example, by providing clear and explicit rules of action. They may deepen deliberation by reinforcing ethical knowledge or understanding. Or they may show how a public health activity is justified, by explaining its ethical basis. As such, public health ethics may provide substantive guidance (ie speak directly to the ethical acceptability of a particular intervention or activity) or procedural guidance (ie direct on the proper steps that have to be followed in order to reach a decision ethically).

Ethical models, meanwhile, provide less reflective guidance and rather provide their users with reminders of particular points of ethical concern. Both frameworks and models are important tools for decision-makers in public health depending on the task and level of complexity involved. When considering the need for these sorts of decision-making tools, it is important to consider what benefit they are intended to serve. Sometimes it will be desirable to refer to a general framework for public health activity articulating values that underpin its mission and overarching objectives. Sometimes a specific framework or model will be appropriate, for example, to aid

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[4] John Coggon, Keith Syrett and A.M. Viens, *Public Health Law: Ethics, Governance and Regulation* (Routledge, 2017), pp. 32-35

decision-making on particular areas or questions, such as pandemic preparedness and response planning.

The development of ethical guidance must take note of three main areas of specificity. First, ethical guidance must be context specific. There are different ethical questions and issues that will arise in different areas of public health work, including policy development and implementation, legislative and regulatory enactment, research, and areas of practice, such as screening, surveillance, health protection and promotion. Core public health functions will require independent ethical attention and, often, different forms of ethical guidance.[5]

Second, ethical guidance must be task specific. For instance, the task of deciding what kind of obesity policy to develop will be different from the task of deciding which particular public health measures should be implemented to reduce obesity. Further still, these tasks will differ from, for instance, devising community engagement/empowerment programmes that directly involve public groups in tackling obesity. Ethical guidance can assist public health workers to undertake each task in a way in which the design, methodologies and implementation are ethically appropriate.

Third, ethical guidance must be level specific. Public health policy-makers and practitioners will have different spheres of influence and will differ in how their activities impact on individuals and populations, which include different levels of power, resource allocation, priority setting and moral responsibility. As such, there is a need for ethical guidance that can take into account the ethical underpinnings of both the influence and impact of different levels of public health action.

[5] See, for instance, Public Health Ontario, A Framework for the Ethical Conduct of Public Health Initiatives (Toronto: Public Health Ontario, 2012)

Case study 3: Pandemic preparedness

In 2007 the Department of Health published Responding to Pandemic Influenza: The Ethical Framework for Policy and Planning. The framework provides a set of ethical principles – respect, harm minimisation, fairness, working together, reciprocity, proportionality, flexibility and good decision-making – that can be used in developing policy and making decisions that act as '…a checklist [that] can help to ensure that the full range of ethical issues is considered' in relation to pandemic influenza.[iii]

As noted above, there are different kinds of ethical frameworks and they can be used in various ways, but using the Responding to Pandemic Influenza framework here can be illustrative of the different reasons why we may want to use ethical frameworks in practice.

If we use this framework for increasing ethical awareness, we can look to these ethical principles to help us to identify and distinguish technical issues from ethical issues (eg the use of restrictive measures, such as quarantine or social distancing, are effective means of reducing infection transmission, but the principle of harm minimisation reminds us that restrictive measures have moral implications and that we should implement these measures in ways that reduce the harm associated with restricting movement).

If we use this framework for assessing ethical justification, we can look to these ethical principles to help us reason through what would provide the best ethical defence of particular polices or interventions (eg the principles of respect, harm minimisation and fairness could be used to justify that everyone in a pandemic has a moral obligation not to infect others and should take all reasonable means to ensure they do not become a vector for influenza).

If using this framework for ethical deliberation, these principles can be used by individuals, such as public health practitioners, to deliberate and guide their action in relation to particular choices (eg the principle of reciprocity can be used within moral deliberation to think through how to balance the increased risks and burdens health care workers face in treating exposed and/or infected patients and what kind of support they should ask for in carrying out this work).

If using this framework for ethical regulation, these principles can be used by policy makers or leaders within institutions to frame and develop policy that governs the action of all practitioners in relation to a particular ethical issue (eg in allocating scarce anti-viral medication, the principle of fairness and good decision-making could favour developing guidelines that individuals who are most vulnerable, such as children and the elderly, should receive priority access to available anti-viral medication before anyone else).

Whether or not an ethical framework can be used in all these ways depends on whether it adequately addresses the context, task and level for which it is being used. Nevertheless, choosing the appropriate ethical tool for the question, issue or topic at hand can provide public health trainees, practitioners and leaders with an ethically defensible framework through which to address policy and practice.

iii Department of Health, Responding to Pandemic Influenza: The Ethical Framework for Policy and Planning (London: DH, 2007), p2

5. Further reading

5.1 General reading

Beauchamp DE, "Public Health as Social Justice," Inquiry (1976) 13(1), 3-14.

Callahan D and Jennings B, "Ethics and Public Health: Forging a Strong Relationship," American Journal of Public Health (2002) 92(2), 169-76.

Coggon J, Syrett K and Viens AM, "Public Health Law – Ethics, Governance, and Regulation" (Routledge, 2017), especially chapter 2.

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5.2 Public health ethics frameworks

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www.apha.org/~/media/files/pdf/about/ethics_brochure.ashx

Tannahill A, "Beyond Evidence – To Ethics: A Decision-Making Framework for Health Promotion, Public Health and Health Improvement." Health Promotion International (2008) 23(4), 380-390.

Upshur R, "Principles for the Justification of Public Health Intervention," Canadian Journal of Public Health (2002) 93:2, 101-103.

A repository of public health ethics frameworks, maintained by the National Collaborating Centre for Healthy Public Policy, is available at:
www.ncchpp.ca/708/Repertoire_of_Frameworks.ccnpps.

Steering group agencies

Association of the Directors of Public Health
Chartered Institute of Environmental Health
Council for the Awards of Care, Health and Education
Department of Health (England)
Faculty of Public Health
Health Education England
Local Government Association
NHS Scotland
Public Health Agency for Northern Ireland
Public Health England
Public Health Wales
Royal College of Midwives
Royal College of Nursing
Royal Society for Public Health
UK Health Forum
UK Public Health Register
University of Brighton

Users' Guides to the Medical Literature

How to Read a Systematic Review and Meta-analysis and Apply the Results to Patient Care

Users' Guides to the Medical Literature

Mohammad Hassan Murad, MD, MPH; Victor M. Montori, MD, MSc; John P. A. Ioannidis, MD, DSc; Roman Jaeschke, MD, MSc; P. J. Devereaux, MD, PhD; Kameshwar Prasad, MD, DM, FRCPE; Ignacio Neumann, MD, MSc; Alonso Carrasco-Labra, DDS, MSc; Thomas Agoritsas, MD; Rose Hatala, MD, MSc; Maureen O. Meade, MD; Peter Wyer, MD; Deborah J. Cook, MD, MSc; Gordon Guyatt, MD, MSc

Clinical decisions should be based on the totality of the best evidence and not the results of individual studies. When clinicians apply the results of a systematic review or meta-analysis to patient care, they should start by evaluating the credibility of the methods of the systematic review, ie, the extent to which these methods have likely protected against misleading results. Credibility depends on whether the review addressed a sensible clinical question; included an exhaustive literature search; demonstrated reproducibility of the selection and assessment of studies; and presented results in a useful manner. For reviews that are sufficiently credible, clinicians must decide on the degree of confidence in the estimates that the evidence warrants (quality of evidence). Confidence depends on the risk of bias in the body of evidence; the precision and consistency of the results; whether the results directly apply to the patient of interest; and the likelihood of reporting bias. Shared decision making requires understanding of the estimates of magnitude of beneficial and harmful effects, and confidence in those estimates.

JAMA. 2014;312(2):171-179. doi:10.1001/jama.2014.5559

Supplemental content at jama.com

CME Quiz at jamanetworkcme.com and **CME Questions** page 186

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Clinical Scenario

You are consulted regarding the perioperative management of a 66-year-old man undergoing hip replacement. He is a smoker and has a history of type 2 diabetes and hypertension. Because he has multiple cardiovascular risk factors, you consider using perioperative β-blockers to reduce the risk of postoperative cardiovascular complications. You identify a recently published systematic review and meta-analysis evaluating the effect of perioperative β-blockers on death, nonfatal myocardial infarction, and stroke.[1] How should you use this meta-analysis to help guide your clinical decision making?

Introduction and Definitions

Traditional, unstructured review articles are useful for obtaining a broad overview of a clinical condition but may not provide a reliable and unbiased answer to a focused clinical question. A systematic review is a research summary that addresses a focused clinical question in a structured, reproducible manner. It is often, but not always, accompanied by a meta-analysis, which is a statistical pooling or aggregation of results from different studies providing a single estimate of effect. **Box 1** summarizes the typical process of a systematic review and meta-analysis including the safeguards against misleading results.

In 1994, a Users' Guide on how to use an "overview article"[2] was published in *JAMA* and presented a framework for critical appraisal of systematic reviews. In retrospect, this framework did not distinguish between 2 very different issues: the rigor of the review methods and the confidence in estimates (quality of evidence) that the results warrant. The current Users' Guide reflects the evolution of thinking since that time and presents a contemporary conceptualization.

We refer to the first judgment as the credibility[3] of the review: the extent to which its design and conduct are likely to have protected against misleading results.[4] Credibility may be undermined by inappropriate eligibility criteria, inadequate literature search, or failure to optimally summarize results. A review with credible methods, however, may leave clinicians with low confidence in effect estimates. Therefore, the second judgment addresses the confidence in estimates.[5] Common reasons for lower confidence include high risk of bias of the individual studies; inconsistent results; and small sample size of the body of evidence, leading to imprecise estimates. This Users' Guide presents criteria for judging both credibility and confidence in the estimates (**Box 2**).

This guide focuses on a question of therapy and is intended for clinicians applying the results to patient care. It does not provide comprehensive advice to researchers on how to conduct[6] or report[7] reviews. We also provide a rationale for seeking systematic reviews and meta-analyses and explaining the summary estimate of a meta-analysis.

Box 1. The Process of Conducting a Systematic Review and Meta-analysis

1. Formulate the question
2. Define the eligibility criteria for studies to be included in terms of Patient, Intervention, Comparison, Outcome (PICO), and study design
3. Develop a priori hypotheses to explain heterogeneity
4. Conduct search
5. Screen titles and abstracts for inclusion
6. Review full text of possibly eligible studies
7. Assess the risk of bias
8. Abstract data
9. When meta-analysis is performed:
   - Generate summary estimates and confidence intervals
   - Look for explanations of heterogeneity
   - Rate confidence in estimates of effect

Box 2. Guide for Appraising and Applying the Results of a Systematic Review and Meta-analysis[a]

First Judgment: Evaluate the Credibility of the Methods of Systematic Review

Did the review explicitly address a sensible clinical question?

Was the search for relevant studies exhaustive?

Were selection and assessments of studies reproducible?

Did the review present results that are ready for clinical application?

Did the review address confidence in estimates of effect?

Second Judgment: Rate the Confidence in the Effect Estimates

How serious is the risk of bias in the body of evidence?

Are the results consistent across studies?

How precise are the results?

Do the results directly apply to my patient?

Is there concern about reporting bias?

Are there reasons to increase the confidence rating?

[a] Systematic reviews can address multiple questions. This guide is applied to aspects of the systematic review that answer the clinical question at hand—ideally the effect of the intervention vs the comparator of interest on all outcomes of importance to patients.

Why Seek Systematic Reviews and Meta-analysis?

When searching for evidence to answer a clinical question, it is preferable to seek a systematic review, especially one that includes a meta-analysis. Single studies are liable to be unrepresentative of the total evidence and be misleading.[8] Collecting and appraising multiple studies require time and expertise that practitioners may not have. Systematic reviews include a greater range of patients than any single study, potentially enhancing confidence in applying the results to the patient at hand.

Meta-analysis of a body of evidence includes a larger sample size and more events than any individual study, leading to greater precision of estimates, facilitating confident decision making. Meta-analysis also provides an opportunity to explore reasons for inconsistency among studies.

A key limitation of systematic reviews and meta-analyses is that they produce estimates that are as reliable as the studies summarized. A pooled estimate derived from meta-analysis of randomized trials at low risk of bias will always be more reliable than that derived from a meta-analysis of observational studies or of randomized trials with less protection against bias.

First Judgment: Was the Methodology of the Systematic Review Credible?

Did the Review Explicitly Address a Sensible Clinical Question?

Systematic reviews of therapeutic questions should have a clear focus and address questions defined by particular patients, interventions, comparisons, and outcomes (PICO). When a meta-analysis is conducted, the issue of how narrow or wide the scope of the question becomes particularly important. Consider 4 hypothetical examples of meta-analyses with varying scope: (1) the effect of all cancer treatments on mortality or disease progression; (2) the effect of chemotherapy on prostate cancer–specific mortality; (3) the effect of docetaxel in castration-resistant prostate cancer on cancer-specific mortality; (4) the effect of docetaxel in metastatic castration-resistant prostate cancer on cancer-specific mortality

These 4 questions represent a gradually narrowing focus in terms of patients, interventions, and outcomes. Clinicians will be uncomfortable with a meta-analysis of the first question and likely of the second. Combining the results of these studies would yield an estimate of effect that would make little sense or be misleading. Comfort level in combining studies increases in the third and fourth questions, although clinicians may even express concerns about the fourth question because it combines symptomatic and asymptomatic populations.

What makes a meta-analysis too broad or too narrow? Clinicians need to decide whether, across the range of patients, interventions or exposures, and outcomes, it is plausible that the intervention will have a similar effect. This decision will reflect an understanding of the underlying biology and may differ between individuals; it will only be possible, however, when systematic reviewers explicitly present their eligibility criteria.

Was the Search for Relevant Studies Exhaustive?

Systematic reviews are at risk of presenting misleading results if they fail to secure a complete or representative sample of the available eligible studies. For most clinical questions, searching a single database is insufficient. Searching MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials may be a minimal requirement for most clinical questions[6] but for many questions will not uncover all eligible articles. For instance, one study demonstrated that searching MEDLINE and EMBASE separately retrieved, respectively, only 55% and 49% of the eligible trials.[9] Another study found that 42% of published meta-analyses included at least 1 trial not indexed in MEDLINE.[10] Multiple synonyms and search terms to describe each concept are needed.

Additional references are identified through searching trial registries, bibliography of included studies, abstract presentations, contacting experts in the field, or searching databases of pharmaceutical companies and agencies such as the US Food and Drug Administration.

Were Selection and Assessments of Studies Reproducible?

Systematic reviewers must decide which studies to include, the extent of risk of bias, and what data to abstract. Although they

follow an established protocol, some of their decisions will be subjective and prone to error. Having 2 or more reviewers participate in each decision may reduce error and subjectivity. Systematic reviewers often report a measure of agreement on study selection and quality appraisal (eg, κ statistic). If there is good agreement between the reviewers, the clinician can have more confidence in the process.

Did the Review Present Results That Are Ready for Clinical Application?

Meta-analyses provide estimates of effect size (the magnitude of difference between groups).[11] The type of effect size depends on the nature of the outcome (relative risk, odds ratio, differences in risk, hazard ratios, weighted mean difference, and standardized mean difference). Standardized effect sizes are expressed in multiples of the standard deviation. This facilitates comparison of studies, irrespective of units of measure or the measurement scale.

Results of meta-analyses are usually depicted in a forest plot. The point estimate of each study is typically presented as a square with a size proportional to the weight of the study, and the confidence interval (CI) is presented as a horizontal line. The combined summary effect, or pooled estimate, is typically presented as a diamond, with its width representing the confidence or credible interval (the CI indicates the range in which the true effect is likely to lie). Forest plots for the perioperative β-blockers scenario are shown in the **Figure**.

Meta-analysis provides a weighted average of the results of the individual studies in which the weight of the study depends on its precision. Studies that are more precise (ie, have narrower CIs) will have greater weight and thus more influence on the combined estimate. For binary outcomes such as death, the precision depends on the number of events and sample size. In panel B of the Figure, the POISE trial[12] had the largest number of deaths (226) and the largest sample size (8351); therefore, it had the narrowest CI and the largest weight (the effect from the trial is very similar to the combined effect). Smaller trials with smaller numbers of events in that plot have a much wider CI, and their effect size is quite different from the combined effect (ie, had less weight in meta-analysis). The weighting of continuous outcomes is also based on the precision of the study, which in this case depends on the sample size and SD (variability) of each study.

In most meta-analyses such as the one in this clinical scenario, aggregate data from each study are combined (ie, study-level data). When data on every individual enrolled in each of the studies are available, individual-patient data meta-analysis is conducted. This approach facilitates more detailed analysis that can address issues such as true intention-to-treat and subgroup analyses.

Relative association measures and continuous outcomes pose challenges to risk communication and trading off benefits and harms. Patients at high baseline risk can expect more benefit than those at lower baseline risk from the same intervention (the same relative effect). Meta-analysis authors can facilitate decision making by providing absolute effects in populations with various risk levels.[13,14] For example, given 2 individuals, one with low Framingham risk of cardiovascular events (2%) and the other with a high risk (28%), we can multiply each of these baseline risks with the 25% relative risk reduction obtained from a meta-analysis of statin therapy trials.[15] The resulting absolute risk reduction (ie, risk difference) attributable to statin therapy would be 0.5% for the low-risk individual and 7% for the high-risk individual.

Continuous outcomes can also be presented in more useful ways. Improvement of a dyspnea score by 1.06 scale points can be better understood by informing readers that the minimal amount considered by patients to be important on that scale is 0.5 points.[16] A standardized effect size (eg, paroxetine reduced depression severity by 0.31 SD units) can be better understood if (1) referenced to cutoffs of 0.2, 0.5, and 0.8 that represent small, moderate, and large effect, respectively; (2) translated back to natural units with which clinicians have more familiarity (eg, converted to a change of 2.47 on the Hamilton Rating Scale for Depression); or (3) dichotomized (for every 100 patients treated with paroxetine, 11 will achieve important improvement).[17]

Did the Review Address Confidence in Estimates of Effect?

A well-conducted (ie, credible) systematic review should present readers with information needed to make their second judgement: the confidence in the effect estimates. For example, if systematic reviewers do not evaluate the risk of bias in the individual studies or attempt to explain heterogeneity, this second judgement will not be possible.

In **Box 3**, we return to the clinical scenario to determine credibility of the systematic review identified. Overall, you conclude that the credibility of the methods of this systematic review is high and move on to examine the estimates of effect and the associated confidence in these estimates.

Second Judgment: What Is the Confidence in the Estimates of Effect?

Several systems are used to evaluate the quality of evidence, of which 4 are most commonly used: the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and the systems from the American Heart Association, the US Preventive Services Task Force, and the Oxford Centre for Evidence-Based Medicine.[5,18-20] These systems share the similar features of being used by multiple organizations and providing a confidence rating in the estimates that gives randomized trials a higher rating than nonrandomized studies. The 4 systems are described in eTable 1 in the Supplement.

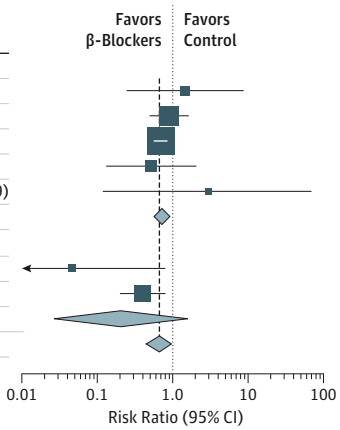
The general framework used in this Users' Guide follows the GRADE approach.[21] GRADE categorizes confidence in 4 categories: high, moderate, low, or very low. The lower the confidence, the more likely the underlying true effect is substantially different from the observed estimate of effect and, thus, the more likely that further research would demonstrate different estimates.[5]

Confidence ratings begin by considering study design. Randomized trials are initially assigned high confidence and observational studies are given low confidence, but a number of factors may modify these initial ratings. Confidence may decrease when there is high risk of bias, inconsistency, imprecision, indirectness, or concern about publication bias. An increase in confidence rating is uncommon and occurs primarily in observational studies when the effect size is large. Readers of a systematic review can consider these factors regardless of whether systematic review authors formally used this approach. Readers do, however, require the necessary information, and thus the need for a final credibility guide: Did the Review Address Confidence in Estimates of Effect?

Figure. Results of a Meta-analysis of the Outcomes of Nonfatal Infarction, Death, and Nonfatal Stroke in Patients Receiving Perioperative β-Blockers

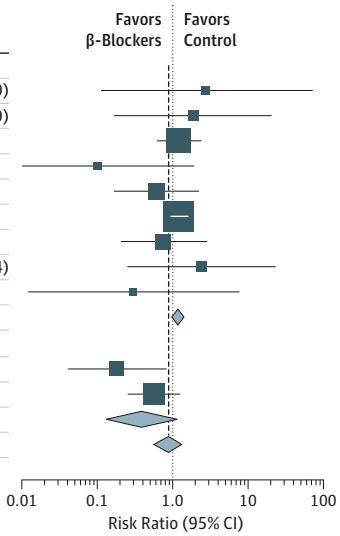
A Nonfatal myocardial infarction

Source	β-Blockers Events, No.	β-Blockers Total, No.	Control Events, No.	Control Total, No.	RR (95% CI)
Low risk of bias					
DIPOM	3	462	2	459	1.49 (0.25-8.88)
MaVS	19	246	21	250	0.92 (0.51-1.67)
POISE	152	4174	215	4177	0.71 (0.58-0.87)
POBBLE	3	55	5	48	0.52 (0.13-2.08)
BBSA	1	110	0	109	2.97 (0.12-72.19)
Subtotal (I^2 = 0%; P = .70)					0.73 (0.61-0.88)
High risk of bias					
Poldermans	0	59	9	53	0.05 (0.00-0.79)
Dunkelgrun	11	533	27	533	0.41 (0.20-0.81)
Subtotal (I^2 = 57%; P = .13)					0.21 (0.03-1.61)
Overall					0.67 (0.47-0.96)
I^2 = 29%; P = .21					
Interaction test between groups, P = .22					



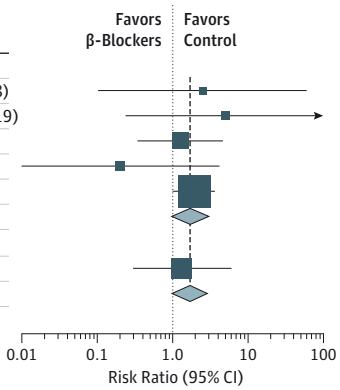
B Death

Source	β-Blockers Events, No.	β-Blockers Total, No.	Control Events, No.	Control Total, No.	RR (95% CI)
Low risk of bias					
BBSA	1	110	0	109	2.97 (0.12-72.19)
Bayliff	2	49	1	50	2.04 (0.19-21.79)
DIPOM	20	462	15	459	1.32 (0.69-2.55)
MaVS	0	246	4	250	0.11 (0.01-2.09)
Neary	3	18	5	20	0.67 (0.19-2.40)
POISE	129	4174	97	4177	1.33 (1.03-1.73)
Mangano	4	99	5	101	0.82 (0.23-2.95)
POBBLE	3	55	1	48	2.62 (0.28-24.34)
Yang	0	51	1	51	0.33 (0.01-8.00)
Subtotal (I^2 = 0%; P = .68)					1.27 (1.01-1.60)
High risk of bias					
Poldermans	2	59	9	53	0.20 (0.05-0.88)
Dunkelgrun	10	533	16	533	0.63 (0.29-1.36)
Subtotal (I^2 = 44%; P = .18)					0.42 (0.15-1.23)
Overall					0.94 (0.63-1.40)
I^2 = 30%; P = .16					
Interaction test between groups, P = .04					



C Nonfatal stroke

Source	β-Blockers Events, No.	β-Blockers Total, No.	Control Events, No.	Control Total, No.	RR (95% CI)
Low risk of bias					
POBBLE	1	53	0	44	2.50 (0.10-59.88)
DIPOM	2	462	0	459	4.97 (0.24-103.19)
MaVS	5	246	4	250	1.27 (0.35-4.67)
Yang	0	51	2	51	0.20 (0.01-4.07)
POISE	27	4174	14	4177	1.93 (1.01-3.68)
Subtotal (I^2 = 0%; P = .60)					1.73 (1.00-2.99)
High risk of bias					
Dunkelgrun	4	533	3	533	1.33 (0.30-5.93)
Overall					1.67 (1.00-2.80)
I^2 = 0%; P = .71					
Interaction test between groups, P = .75					



Abbreviations: BBSA, Beta Blocker in Spinal Anesthesia study; DIPOM, Diabetic Postoperative Mortality and Morbidity trial; MaVS, Metoprolol after Vascular Surgery study; POBBLE, Perioperative β-blockade trial; POISE, Perioperative Ischemic Evaluation trial. Dotted line indicates no effect. Dashed line is centered on meta-analysis pooled estimate.

How Serious Is the Risk of Bias in the Body of Evidence?

A well-conducted systematic review should always provide readers with insight about the risk of bias in each individual study and overall.[6,7] Differences in studies' risk of bias can explain important differences in results.[22] Less rigorous studies sometimes overestimate the effectiveness of therapeutic and preventive interventions.[23] The effects of antioxidants on the risk of prostate cancer[24] and on atherosclerotic plaque formation[25] are 2 of many

Box 3. Using the Guide: Judgment 1, Determining Credibility of the Methods of a Systematic Review (Perioperative β-Blockers in Noncardiac Surgery)[1]

Systematic review authors constructed a sensibly structured clinical question (in patients at higher-than-average cardiovascular risk undergoing noncardiac surgery, what is the effect of β-blockers vs no β-blockers on nonfatal myocardial infarction, death, and stroke)

They conducted a comprehensive search of numerous databases and registries

Two independent reviewers selected eligible trials, although the authors did not report extent of agreement

The authors ultimately presented results in a transparent and understandable way. Although they did not report an absolute effect—an important limitation—the raw data allow readers to easily calculate an absolute effect and a number needed to treat (Box 4 and Table).

The authors provided the information needed to address confidence in study results. They described the risk of bias for each trial, noted substantial heterogeneity in estimates of the effect of β-blockers on death, determined that risk of bias provided a likely explanation for the variability, and therefore focused on the results of the studies with low risk of bias.

examples of observational studies that showed misleading results subsequently contradicted by large randomized clinical trials.

Ideally, systematic reviewers will evaluate and report the risk of bias for each of the important outcomes measured in each individual study. There is no one correct way to assess the risk of bias.[26] Review authors can use detailed checklists or focus on a few key aspects of the study. Different study designs require the use of different instruments (eg, for randomized clinical trials, the Cochrane Risk of Bias Tool[27]). A judgment about the overall risk of bias for all of the included studies may then result in decreasing the confidence in estimates.[5]

Are the Results Consistent Across Studies?

Readers of a meta-analysis that combines results from multiple studies should judge the extent to which results differ from study to study (ie, variability or heterogeneity). They can start by visually inspecting a forest plot,[28] first noting differences in the point estimates and then the extent to which CIs overlap. Large differences in point estimates or CIs that do not overlap suggest that random error is an unlikely explanation of the different results and therefore decreases confidence in the combined estimate.

Authors of a meta-analysis can help readers by conducting statistical evaluation of heterogeneity (eTable 2 in the Supplement). The first test is called the Cochran Q test (a yes-or-no test), in which the null hypothesis is that the underlying effect is the same in each of the studies[29] (eg, the relative risk derived from study 1 is the same as that from studies 2, 3, and 4). A low *P* value of the test means that random error is an unlikely explanation for the differences in results from study to study, thus decreasing confidence in a single summary estimate.

The I^2 statistic focuses on the magnitude of variability rather than its statistical significance.[30] An I^2 of 0% suggests that chance explains variability in the point estimates, and clinicians can be comfortable with a single summary estimate. As the I^2 increases, we become progressively less comfortable with unexplained variability in results.

When substantial heterogeneity exists, clinicians should look for possible explanations. Authors of meta-analyses may conduct subgroup analyses to explain heterogeneity. Such analyses may not reflect true subgroup differences, and a Users' Guide is available to aid readers in evaluating the credibility of these analyses.[7] Authors of meta-analyses can address one important credibility criterion, whether chance can explain differences between subgroups, using what is called a test of interaction.[31] The lower the *P* value of the test of interaction, the less likely chance explains the difference between intervention effects in the subgroups examined, and therefore the greater likelihood that the subgroup effect is real.

Another approach to exploring causes of heterogeneity in meta-analysis is meta-regression. Investigators construct a regression model in which independent variables are individual study characteristics (eg, the population, how the intervention was administered) and the dependent variable is the estimate of effect in each study. Conclusions from meta-regression have the same limitations as those from subgroup analysis, and inferences about explanations of heterogeneity may not be accurate. For example, meta-regression[32] of trials evaluating statin therapy in patients undergoing percutaneous interventions for acute coronary syndrome showed that the earlier statins were given, the lower the risk of cardiac events. Although the trials were randomized (to statin vs no statin or a lower-dose statin), the conclusion about early administration was not based on randomization and should be evaluated using the Users' Guide on subgroup analysis.[7]

It is not uncommon that a large degree of between-study heterogeneity remains unexplained. Clinicians and patients still need, however, a best estimate of the treatment effect to inform their decisions. Pending further research that may explain the observed heterogeneity, the summary estimate remains the best estimate of the treatment effect. Clinicians and patients must use this best available evidence, although this inconsistency between studies appreciably reduces confidence in the summary estimate.[33]

In the β-blocker meta-analysis, the risk of bias explains variability in results in the outcome of death (Figure, panel B). Results are very different for the trials with high and low risk of bias, and the *P* value for the test of interaction (.04) tells us that chance is an unlikely explanation for the difference. Therefore, we use the results from the trials with low risk of bias as our best estimate of the treatment effect.

How Precise Are the Results?

There are 2 fundamental reasons that studies mislead: one is systematic error (otherwise known as bias), and the other is random error. Random error is large when sample sizes, and numbers of events, are small, and decreases as sample size and number of events increase. When sample size and number of events are small, we refer to results as "imprecise"; when they are large, we label results as "precise."

When results are imprecise, we lose confidence in estimates of effect. But how is the clinician to determine if results are sufficiently precise? Meta-analysis generates not only an estimate of the average effect across studies, but also a CI around that estimate. Examination of that CI—the range of values within which the true effect plausibly lies—allows a judgement of whether a meta-analysis yields results that are sufficiently precise.

Clinicians can judge precision by considering the upper and lower boundaries of the CI and then considering how they would advise

Box 4. Using the Guide: Judgment 2, Determining the Confidence in the Estimates (Perioperative β-Blockers in Noncardiac Surgery)[1]

See the Table for the raw data used in this discussion.

How to Calculate Risk Difference (Absolute Risk Reduction or Increase)?

In the Figure, the risk ratio (RR) for nonfatal myocardial infarction is 0.73. The baseline risk (risk without perioperative β-blockers) can be obtained from the trial that is the largest and likely enrolled most representative population[12] (215/4177, approximately 52 per 1000). The risk with intervention would be (52/1000 × 0.73, approximately 38 per 1000). The absolute risk difference would be (52/1000 − 38/1000 = −14, approximately 14 fewer myocardial infarctions per 1000). The same process can be used to calculate the confidence intervals around the risk difference, substituting the boundaries of the confidence interval (CI) of the RR for the point estimate.

The number needed to treat to prevent 1 nonfatal myocardial infarction can also be calculated as the inverse of the absolute risk difference (1/0.014 = 72 patients).

Risk of Bias

Of the 11 trials included in the analysis, 2 were considered to have high risk of bias.[35,36] Limitations included lack of blinding, stopping early because of large apparent benefit,[36] and concerns about the integrity of the data.[1] The remaining 9 trials had adequate bias protection measures and represented a body of evidence that was at low risk of bias.

Inconsistency

Visual inspection of forest plots (Figure) shows that the point estimates, for both nonfatal myocardial infarction and death, substantially differ across studies. For the outcome of stroke, results are extremely consistent. There is minimal overlap of CIs of point estimates for the analysis of death. Confidence intervals in the analysis of nonfatal myocardial infarction do overlap to a great extent and fully overlap in the outcome of stroke. Heterogeneity *P* values were .21 for nonfatal myocardial infarction, .16 for death, and .71 for stroke; I^2 values were 29%, 30%, and 0%, respectively. A test of interaction between the 2 groups of studies (high risk of bias vs low risk of bias) yields a nonsignificant *P* value of .22 for myocardial infarction (suggesting that the difference between these 2 subgroups of studies could be attributable to chance) and a significant *P* value of .04 for the outcome of death. Considering that the observed heterogeneity is at least partially explained by the risk of bias and that the trials with low risk of bias for all outcomes are consistent, you decide to obtain the estimates of effect from the trials with low risk of bias and do not lower the confidence rating because of inconsistency.

Imprecision

For the outcomes of death and nonfatal stroke, clinical decisions would differ if the upper vs the lower boundaries of the CI represented the truth; therefore, imprecision makes us lose confidence in both estimates. No need to lower the confidence rating for nonfatal myocardial infarction.

Indirectness

The age of the majority of patients enrolled across the trials ranged between 50 and 70, similar to the patient in the opening scenario, who is 66 years old. Most of the trials enrolled patients with risk factors for heart disease undergoing surgical procedures classified as intermediate surgical risk, similar to the risk factors and hip surgery of the patient. Although the drug used and the dose varied across trials, the consistent results suggest we can use a modest dose of the β-blocker with which we are most familiar. The outcomes of death, nonfatal stroke, and nonfatal infarction are the key outcomes of importance to patients. Overall, the available evidence presented in the systematic review is direct and applicable to the patient of interest and addresses the key outcomes.

Reporting Bias

The authors of the systematic review and meta-analysis constructed funnel plots that appear to be symmetrical and results of the statistical tests for the symmetry of the plot were nonsignificant, leaving no reason for lowering the confidence rating because of possible reporting or publication bias.

Confidence in the Estimates

Overall, evidence warranting high confidence suggests that individuals with risk factors for heart disease can expect a reduction in risk of a perioperative nonfatal infarction of 14 in 1000 (from approximately 20 per 1000 to 6 per 1000). Unfortunately, they can also expect an increase in their risk of dying or having a nonfatal stroke. Because most people are highly averse to stroke and death, it is likely that the majority of patients faced with this evidence would decline β-blockers as part of their perioperative regimen. Indeed, that is what this patient decides when informed about the evidence.

Table. Evidence Summary of the Perioperative β-Blockers Question

Outcome	No. of Participants (Trials)	Confidence	Relative Effect (95% CI)	Risk Difference per 1000 Patients[a]
Nonfatal myocardial infarction	10 189 (5)	High	0.73 (0.61-0.88)	14 fewer (6 fewer to 20 fewer)
Stroke	10 186 (5)	Moderate	1.73 (1.00- 2.99)	2 more (0 more to 6 more)
Death	10 529 (9)	Moderate	1.27 (1.01-1.60)	6 more (0 more to 13 more)

[a] See Box 4.

their patients were the upper boundary to represent the truth and how they would advise their patients were the lower boundary to represent the truth. If the advice would be the same in either case, then the evidence is sufficiently precise. If decisions would change across the range of the confidence interval, then confidence in the evidence will decrease.[34]

For instance, consider the results of nonfatal myocardial infarction in the β-blocker example (**Box 4** and **Table**). The CI around the absolute effect of β-blockers is a reduction of from 6 (the minimum) to 20 (the maximum) infarctions in 1000 patients given β-blockers. Considering this range of plausible effects, clinicians must ask themselves: Would my patients make different choices about

the use of β-blockers if their risk of infarction decreased by only 6 in 1000 or by as much as 20 in 1000?

One might readily point out that this judgment is subjective—it is a matter of values and preferences. Quite so, but that is the nature of clinical decision making: the trade-off between the desirable and undesirable consequences of the alternative courses of action is a matter of values and preferences and is therefore subjective. To the extent that clinicians are confident that patients would place similar weight on reductions of 6 and 20 in 1000 infarctions, concern about imprecision will be minimal. To the extent that clinicians are confident that patients will view 6 in 1000 as trivial and 20 in 1000 as important, concern about imprecision will be large. To the extent that clinicians are uncertain of their patients' values and preferences on the matter, judgments about imprecision will be similarly insecure.

The judgment regarding myocardial infarction may leave clinicians with doubt about imprecision—much less so for stroke and death (Box 4 and Table). With regard to both, if the boundary most favoring β-blockers (ie, no increase in death and stroke) represented the truth, patients would have no reluctance regarding use of β-blockers. On the other hand, if risk of death and stroke increased by, respectively, 13 and 6, reluctance regarding use of β-blockers would increase substantially. Given uncertainty about which extreme represents the truth, confidence in estimates decreases because of imprecision.

Do the Results Directly Apply to My Patient?

The optimal evidence for decision making comes from research that directly compared the interventions in which we are interested, evaluated in the populations in which we are interested, and measured outcomes important to patients. If populations, interventions, or outcomes in studies differ from those of interest, the evidence can be viewed as indirect.

A common example of indirectness of population is when we treat a very elderly patient using evidence derived from trials that excluded elderly persons. Indirectness of outcomes occurs when trials use surrogate end points (eg, hemoglobin A_{1c} level), whereas patients are most concerned about other outcomes (eg, macrovascular and microvascular disease).[37] Indirectness also occurs when clinicians must choose between interventions that have not been tested in head-to-head comparisons.[38] For instance, many trials have compared osteoporosis drugs with placebo, but very few have compared them directly against one another.[39] Making comparisons between treatments under these circumstances requires extrapolation from existing comparisons and multiple assumptions.[40]

Decisions regarding indirectness of patients and interventions depend on an understanding of whether biologic or social factors are sufficiently different that one might expect substantial differences in the magnitude of effect. Indirectness can lead to lowering confidence in the estimates.[38]

Is There Concern About Reporting Bias?

When researchers base their decision to publish certain material on the magnitude, direction, or statistical significance of the results, a systematic error called reporting bias occurs. This is the most difficult type of bias to address in systematic reviews. When an entire study remains unreported, the standard term is publication bias. It has been shown that the magnitude and direction of results may be more important determinants of publication than study design, relevance, or quality[41] and that positive studies may be as much as 3 times more likely to be published than negative studies.[42] When authors or study sponsors selectively report specific outcomes or analyses, the term selective outcome reporting bias is used.[43]

Empirical evidence suggests that half of the analysis plans of randomized trials are different in protocols than in published reports.[44] Reporting bias can create misleading estimates of effect. A study of the US Food and Drug Administration reports showed that they often included numerous unpublished studies and that the findings of these studies can alter the estimates of effect.[45] Data on 74% of patients enrolled in the trials evaluating the antidepressant reboxetine were unpublished. Published data overestimated the benefit of reboxetine vs placebo by 115% and vs other antidepressants by 23%, and also underestimated harm.[46]

Detecting publication bias in a systematic review is difficult. When it includes a meta-analysis, a common approach is to examine whether the results of small studies differ from those of larger ones. In a figure that relates the precision (as measured by sample size, SE, or variance) of studies included in a meta-analysis to the magnitude of treatment effect, the resulting display should resemble an inverted funnel (eFigure, panel A in the Supplement). Such funnel plots should be symmetric around the combined effect. A gap or empty area in the funnel suggests that studies may have been conducted and not published (eFigure, panel B in the Supplement). Other explanations for asymmetry are, however, possible. Small studies may have a higher risk of bias explaining their larger effects, may have enrolled a more responsive patient group, or may have administered the intervention more meticulously. Last, there is always the possibility of a chance finding.

Several empirical tests have been developed to detect publication bias. Unfortunately, all have serious limitations, require a large number of studies (ideally 30 or more),[47] and none has been validated against a criterion standard of real data in which we know whether bias existed.[47]

More compelling than any of these theoretical exercises is the success of systematic reviewers in obtaining the results of unpublished studies. Prospective study registration with accessible results may be a solution to reporting bias.[48,49] Until complete reporting becomes a reality,[50] clinicians using research reports to guide their practice must remain cognizant of the dangers of reporting biases and, when they suspect bias, should lower their confidence in the estimates.[51]

Are There Reasons to Increase the Confidence Rating?

Some uncommon situations warrant an increase in the confidence rating of effect estimates from observational studies. Consider our confidence in the effect of hip replacement on reducing pain and functional limitations in severe osteoarthritis, epinephrine to prevent mortality in anaphylaxis, insulin to prevent mortality in diabetic ketoacidosis, or dialysis to prolong life in patients with end-stage renal failure.[52] In each of these situations, we observe a large treatment effect achieved over a short period among patients with a condition that would have inevitably worsened in the absence of an intervention. This large effect can increase confidence in a true association.[52]

Box 4 and the Table summarize the effect of β-blockers in patients undergoing noncardiac surgery and addresses our confidence in the apparent effects of the intervention.

Conclusions

Clinical and policy decisions should be based on the totality of the best evidence and not the results of individual studies. Systematic summaries of the best available evidence are required for optimal clinical decision making. Applying the results of a systematic review and meta-analysis includes a first step in which we judge the credibility of the methods of the systematic review and a second step in which we decide how much confidence we have in the estimates of effect.

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Author Contributions: Dr Murad had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Drs Murad and Montori receive funding from several non-for-profit organizations to conduct systematic reviews and meta-analysis. The Meta-Research Innovation Center at Stanford (METRICS), directed by Dr Ioannidis, is funded by a grant from the Laura and John Arnold Foundation. Dr Agoritsas was financially supported by Fellowship for Prospective Researchers Grant No. PBGEP3-142251 from the Swiss National Science Foundation. Dr Cook is a Research Chair of the Canadian Institutes of Health Research.

Disclaimer: Drs Murad, Montori, Jaeschke, Prasad, Carrasco-Labra, Neumann, Agoritsas, and Guyatt are members of the GRADE Working Group.

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Supplementary Online Content

Murad MH, Montori VM, Ioannidis JPA, et al. How to read a systematic review and meta-analysis and apply the results to patient care. JAMA. doi:10.1001/jama.2014.5559

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 2. Systems Commonly Used for Rating the Quality of Evidence (Confidence in Estimates)†

System	Description
The Grading of Recommendations Assessment, Development and Evaluation (GRADE)[1]	**4 Levels of quality of evidence (confidence in estimates):** • High • Moderate • Low • Very low RCTs start as high and observational studies start as low, then multiple factors that can raise or lower confidence are applied to reach a final rating. **Strength of recommendation:** 1 (strong) or 2 (weak)
American College of Cardiology Foundation/American Heart Association (ACCF/AHA)[2]	**Certainty in evidence:** • level A evidence is derived from multiple RCTs or meta-analyses • level B is derived from a single RCT or nonrandomized studies • level C is derived from consensus opinion of experts, case studies, or standards of care **Classification of Recommendations**: Class I, Class II, , Class IIa, Class IIb, Class III
U.S. Preventive Services Task Force (USPSTF)[3]	**Level of Certainty:** • High: The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies. • Moderate: The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: o The number, size, or quality of individual studies. o Inconsistency of findings across individual studies. o Limited generalizability of findings to routine primary care practice. o Lack of coherence in the chain of evidence. • Low: The available evidence is insufficient to assess effects on health outcomes. **Strength of recommendation**: A, B, C, D, I

The Oxford Centre for Evidence-Based Medicine (version 2, updated in 2011)[4]	**Level of evidence:¶** 1: Systematic review of randomized trials or n-of-1 trials 2: Randomized trial or observational study with dramatic effect 3: Non-randomized controlled cohort/follow-up study 4: Case-series, case-control studies, or historically controlled studies 5: Mechanism-based reasoning

† Other systems exist but the 4 described here are the most commonly used.
¶ The presented description pertains to a therapy benefit question, slight modifications are suggested for other types of questions
Abbreviations: randomized controlled trial (RCT)

eTable References

1. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol.* 2011;64(4):401-406.
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eTable2. The Two Commonly Used Measures to Evaluate Heterogeneity

Cochran *Q*

Cochran *Q test* assumes the null hypothesis that all the apparent variability between individual study results is due to chance. A probability is generated based on a χ^2 distribution, that between-study differences in results equal to or greater than those observed are likely to occur simply by chance.

Interpretation: The smaller the p-value, the less the likelihood that chance alone can explain the differences in results from study to study.

The I^2 Statistic

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

Q is Cochrane Q statistic and df are the degrees of freedom

Negative values of I^2 are considered equal to 0, so that the range of I^2 values is between 0% and 100%.

Interpretation: I^2 represents the percentage of variability in the effect estimate that is due to heterogeneity rather than sampling error (chance). A larger number denotes greater heterogeneity.

eFigure. Funnel Plot to Evaluate for Publication Bias

Panel A (Top), Plot showing no publication bias. Panel B (Bottom), Plot showing possible publication bias

In penal A, the circles represent the point estimates of the trials. The pattern of distribution resembles an inverted funnel. Larger studies tend to be closer to the summary estimate (vertical dashed line). In this case, the effect sizes of the smaller studies are more or less symmetrically distributed around the summary estimate. In panel B, the smaller studies are not symmetrically distributed around either the point estimate (dominated by the larger trials) or the results of the larger trials themselves. The trials expected in the bottom right quadrant are missing. This suggests publication bias and an overestimate of the treatment effect relative to the underlying truth.