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International Policy Frameworks for Consent in Minimal-risk Pragmatic Trials

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ABSTRACT

There is intense debate around the use of altered and waived consent for pragmatic trials. Those in favor argue that traditional consent compromises the internal and external validity of these trials. Those against, warn that the resultant loss of autonomy compromises respect for persons and could undermine trust in the research enterprise.

This article examines whether international ethical guidelines and the policy frameworks in three countries—the United States, England, and Australia—permit altered and waived consent for minimal-risk pragmatic trials conducted outside the emergency setting. Provisions for both are clearly articulated in U.S. regulations, but many countries do not have equivalent frameworks. Investigators should not assume that all consent models permitted in the United States are legal in their jurisdictions, even if they are deemed ethically defensible.

The authors summarize ethical and regulatory considerations and present a framework for investigators contemplating trials with altered or waived consent.

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Clinical research is our primary tool for evaluating health care; it is the method by which we innovate and create or refute evidence of utility for new and existing interventions. The highest level of clinical evidence comes from randomized controlled trials or meta-analyses of robust trials,[1] but these are expensive and time-consuming and there will never be enough of them to address even a small fraction of the important questions health services need to answer.

Alternatives to conventional randomized trials are thus of considerable interest. Novel designs have emerged that maintain the scientific rigor of randomized controlled trials while incorporating the real-world nature of observational studies.[2,3] Features such as real-time randomization at point of care,[1,4,5] with the collection of trial data from electronic health records[4] or clinical registries,[6] enable these trials to rapidly enroll large numbers of participants at considerably reduced cost.

Many such studies fall into the category of comparative effectiveness trials generally defined as head-to-head comparisons of commonly used clinical or public health interventions. Unlike traditional trials that evaluate efficacy in a well-defined and controlled setting, comparative effectiveness trials measure effectiveness—that is, the benefit of interventions in routine clinical practice. Their primary goal is to inform decision-making by providers and policymakers. Internationally, efforts are underway to strengthen capacity to undertake large-scale pragmatic comparative effectiveness trials.[7,8]

In this article, we provide an overview of contemporary thinking on the use of altered or waived consent for pragmatic comparative effectiveness trials; herein referred to as pragmatic trials.

To help investigators formulate their positions on the ethical acceptability of altered or waived consent, we summarize the ethical debate surrounding the use of these models and confirm which international ethical guidelines support their use.

We then establish whether the policy frameworks in three culturally similar countries—the United States, England, and Australia—permit six discrete consent models where consent is simplified, altered, or waived altogether. These countries were selected because, collectively, the authors have experience conducting trials in all three and are familiar with their policy frameworks. We cover both *regulated trials* (those under the purview of the U.S. Food and Drug Administration, the Medicines and Healthcare products Regulatory Agency in the United Kingdom, and the Therapeutic Goods Administration in Australia) *and nonregulated trials* governed by other legislation, federal policy, national guidance, or common law. We exclude trials conducted in emergency settings where patients are incapacitated, as altered consent in that context is already well established in many countries.

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We then explore the reasons for the reported variability in ethics committee decisions around the use of altered or waived consent, including difficulties interpreting preconditions that must be satisfied before these models are permitted. We illustrate how these models have been operationalized by presenting three trials granted an alteration or waiver of consent.

Finally, we summarize key features and considerations into a framework for investigators planning the use of these models for their trials.

Ethical Debate

The current ethical framework for clinical research has emerged over the last century in response to a series of scandals such as the Tuskegee syphilis studies and atrocities committed during the Second World War.[9] A key advance came in 1964 with the Declaration of Helsinki by the World Medical Association which positioned full disclosure and individual autonomy at the heart of ethical research.[10] In the United States, the Belmont Report further clarified the principles to guide the resolution of ethical problems arising from human research by promulgating three ethical principles: *respect for persons* (including the requirement to acknowledge and respect autonomy); *beneficence* (including society's moral obligation to do good to others); and *justice* (including the fair distribution of the benefits and burdens of research and the obligation to address inequalities in health care).[11]

These documents codify the inherent tension between protecting individuals' rights and doing research to support evidence-based care. For most trials, informed consent satisfies ethical mandates while allowing necessary research, but due to the very nature of some pragmatic trials, many experts report that traditional consent can compromise trial integrity or can render a trial impracticable for other reasons (table 1).[12–15] Thus, there is growing consensus that traditional consent may poorly suit pragmatic trials.[16–20] Some experts also question whether traditional consent is ethically necessary when existing practice is being evaluated.[21–24] Others note that lengthy and legalistic approaches to informed consent for minimal risk trials may result in an "injurious misconception," where trial entry is rejected by potential participants because of an exaggerated and disproportionate perception of risk.[23,25]

The debate surrounding informed consent for pragmatic trials is hardly new. It has been more than 30 yr since Chalmers *et al.*[26,27] articulated a confused ethical analysis:

> Illogically, and with no empirical evidence, to support it, a mischievous view has been promoted that the interests of the vast number of patients involved in the poorly controlled experiments of informal medical 'tinkering' are less in need of protection than those of the relatively small number of patients who are involved in planned, properly controlled clinical experiments.

More recently, the debate has been reinvigorated by recognition that both altered and waived consent models are fundamental to the successful development of a "learning healthcare system"; a concept first proposed by the Institute of Medicine,[28] in which knowledge generation processes are embedded into daily practice to continually improve care and deliver value. In essence, altered or waived consent would reduce disruption to normal clinical workflows, making trial integration into routine practice much more feasible. Thus, a number of groups have considered how informed consent could be adapted in such a health system. Kim and Miller propose a model that integrates research consent with the routine clinical discussion with patients.[29] Modi *et al.* advocate routine randomization as the default position and make the case for altered consent.[23] Myles *et al.* have adopted an altered consent model using postrandomization opt-out from further participation.[24] And finally, Faden *et al.* propose a new ethical framework where rigorous, systematic evaluation is considered part of normal practice and where patients and the public are better informed and accept that in some circumstances, individual consent may not be obtained.[30]

Thus, experts appear undecided on the most appropriate models, particularly around the use of waiver of consent.[31] While many accept that for some trials a waiver may be necessary, two camps have emerged:

- Those who feel that *respect for persons* is the overriding ethical principle: *waiver of consent is categorically indefensible in trials or should be limited to those trials that are minimal risk and truly impracticable without it.*
- Those who feel that although *respect for persons* is the central ethical principle, it is not the only ethical principle and cannot be considered in isolation: *waiver of consent should be accepted in a wider group of minimal risk trials.*

International Ethical Guidelines

So how do international guidelines address the tensions between the rights of individuals and the needs of society and do they clarify when a *prima facie* duty such as respect for autonomy can be overridden by other obligations? Arguably, the Declaration of Helsinki is the most influential guideline. It permits research "without prior consent" in the emergency setting, but maintains the voluntary consent requirement for other types of clinical trial. However, the Declaration does permit investigators to, "*consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries.*" The absence of a specific framework for minimal risk trials has prompted others to codify a set of ethical principles. For example, the Ottawa Statement[32] guides the ethical design and conduct of cluster randomized trials and acknowledges that when certain criteria are met, an ethics committee may alter or waive consent. This guidance highlights other relevant considerations such as, "*Who is the subject when an intervention is applied at an organizational level?*" This illustrates the complexity of the

Table 1. Challenges Associated with Traditional Consent

Pragmatic Trial Feature	Challenge Posed by Traditional Consent
Size: Large	The cost of traditional consent makes large trials infeasible without excessive use of public funds.
Study Design: Often cluster designs	Where patients cannot be identified before cluster assignment, individual choice may be impossible to accommodate rendering consent to receive the intervention meaningless.
	When group assignment is known to patients before enrollment, informed consent could result in imbalances in participant characteristics across treatment groups
	Contamination (that cluster designs try to avoid) may still occur if patients in the control arm that are given trial information, become more similar to patients in the intervention arm.
Study Population: Heterogeneous	Traditional consent is a barrier to unselected participant recruitment. Differences between consenting and non-consenting groups may degrade trial validity and limit a trial's ability to generate real-world evidence.
Setting: Usual care	The disruption to clinical workflows caused by traditional consent makes some pragmatic trials logistically impracticable.
Risk: Often minimal	An exaggerated and disproportionate perception of risk when traditional consent is used may increase consent bias.

ethical decision-making process when these models of consent are being considered.

International Council for Harmonisation Good Clinical Practice Guidelines (Good Clinical Practice)[33] require written informed consent covering 20 elements. Although this guideline was primarily developed for "premarket" trials, its wide application to pragmatic trials has been criticized as a threat to their conduct,[34] although lobbying by an international group of investigators[35] may influence its proposed "renovation."[36]

The International Ethical Guidelines for Health-related Research Involving Humans, prepared by the Council for International Organizations of Medical Sciences and the World Health Organization,[37] describes suitable conditions under which an ethics committee may grant a waiver of consent. It recommends the use of three key criteria to support ethics committee decision-making:

> A research ethics committee may waive informed consent if it is convinced that the research would not be feasible or practicable to carry out without the waiver, the research has important social value, and the research poses no more than minimal risks toward participants.

Policy Frameworks

The policy frameworks in the United States, England, and Australia describe several discrete consent models using a variety of terminology. In addition to the terms "simplified consent," "altered consent," and "waived consent," the terms "broadcast consent," "opt-out," "limited disclosure," and "deemed consent" are also used to describe aspects of these models. To enable comparison, we define six consent submodels representing the "best fit" across these countries (table 2).

Discordance in Policy Frameworks

Our analysis of policy frameworks and associated regulation (Supplemental Digital Content, http://links.lww.com/ALN/C77) quantifies the discordance across regulatory frameworks. In summary, the United States permits all six models in table 2 for both regulated and nonregulated trials when certain preconditions are met. These models are sanctioned by clear, research-specific policy. Although Australia has no national guidance that explicitly endorses the use of altered or waived consent for minimal risk trials, all six models appear to be permitted for nonregulated trials

Table 2. Models of Consent

Consent Models		Description
Simplified Consent	1	The information given to patients is simplified (*e.g.,* fewer pages): retains all content required by national policy but omits some elements currently requested by ethics committees (*e.g.,* some of the elements required by Good Clinical Practice).
	2	The process is simplified (*e.g.*, verbal consent).
Altered Consent	3	The information given to patients is altered: omits some elements generally required by national policy.
	4	The process is altered: trial information is disseminated before trial entry (*e.g.,* poster or leaflet in admission pack) so that patients may opt-out. Patients provide a verbal/written affirmative agreement either before randomization or after randomization (consent to continue).
Waiver of Consent	5*	Trial information is disseminated before trial entry (*e.g.*, poster or leaflet in admission pack) so that patients may opt-out, but there is no requirement for patients to provide an affirmative agreement to trial entry (also termed general approval or broadcast notification).
	6	No requirement to disseminate information to patients or to seek consent.

*Submodel 5 is neither consent nor an outright waiver.

and regulated trials through *de facto* provisions. In contrast, if England adopts the European Clinical Trials Regulation[38] post-Brexit, waiver of consent will not be permitted in any situation other than the emergency setting and altered (opt-out) consent will only be permitted for a subset of cluster trials. Consent forms may be simplified, but verbal consent for trials will rarely be permitted. For nonregulated trials, only simplified consent is endorsed by explicit trial guidance.

In England and Australia, the limited use of altered and waived consent may, in part, be due to the absence of clear, trial-specific policy. In both countries, investigators and ethics committees considering the use of these models are left to interpret an array of legislation. To establish a defensible position, they must "deconstruct" informed consent into its component parts: (1) consent to process data; (2) consent to treatment: and (3) consent to enter a trial. In both countries, mechanisms exist that allow waiver of consent to process data for research. In both countries, there are common law requirements for consent to treatment that require disclosure of material risk and reasonable alternatives which for pragmatic trials would mirror what would have been appropriate outside the trial setting. For waiver of consent to disclose trial entry, common law requires patients to understand *the nature and purpose* of the treatment being offered. If, for individual trials, patients are not made aware of the *research purpose* (namely to generate better evidence through "randomization"), patient engagement through trial awareness activities should be considered. For example, the widespread broadcast of an institution's reasons and arguments for embedding trials into routine care would increase awareness that trials are conducted primarily to improve care. If patients understand and accept that the goals of research (generating knowledge) and the goals of clinical care (treating patents) are converging, the risks related to nondisclosure of the research component of treatment and its adverse impact on patient autonomy would be minimized.

Variability in Ethics Committee Decisions

One common theme in the literature is the lack of consistency in ethics committee decisions around the use of altered and waived consent, particularly in the United States where these models are most widely used.[39–40,17] We present three trials (two from the United States and one from Australia) that illustrate how investigators justify the use of alteration or waiver of consent (table 3). We also discuss why ethics committees have difficulty interpreting the preconditions present in the legislation that must be satisfied before these models; particularly waiver of consent can be used.

Much of the variation in ethics committee decision-making is attributed to the wide interpretation of two key preconditions present in both research and privacy regulation: the requirement for trial risk to be *minimal* and the requirement for the trial to be *impracticable* without alteration or waiver of consent.

What Makes a Trial Minimal Risk?

An ethics committee needs adequate information about the relative risk of a patient's treatment inside and outside the trial. But how should they use this information to determine trial risk? Without clear guidance, ethics committees may well question how a trial involving the use of high dose dexamethasone during open heart surgery (Trial 1) could ever be considered low risk. Lantos *et al.* make a strong case that the risks posed by existing standard of care (which in Trial 1 was high dose dexamethasone) should not be part of the trial risk determination.[39] Importantly, all three countries in our review support this position and have attempted to provide clarity. Table 4 provides extracts from national policy or guidance that directs ethics committees to consider "trial risk" as the risk that is incremental to the risk posed by standard medical care for the condition being treated.

However, Kim and Miller have cautioned that even if the incremental risk is low, nondisclosure of trial entry may adversely affect patient welfare if the treatments being compared have different types of risks and benefits that would be important to patients, as would be the case for a trial comparing sedation *versus* general anesthesia or open *versus* laparoscopic surgery.[41] Welfare concerns may also diminish if patients have no real choice outside the trial. This is especially true for trials investigating components of complex interventions where in routine practice, tacit consent is assumed. This is illustrated in Trial 2 where the oxygen concentration chosen for surgery would neither be discussed nor subject to patient choice. As is commonly the case with all clinical trials, welfare considerations are especially relevant when trials involve disenfranchised or disadvantaged populations who may be less able to express free choice about participation. For example, poor literacy would render some consent models unsuitable. Investigators and ethics committees should consider whether special protections are needed for such participants.[32]

Trial 1 illustrates that it may be appropriate to make independent risk determinations for individual study arms (rather than the whole trial). Such provisions can be found in both the United States and Australian guidance.[42,43]

What Makes a Trial Impracticable?

In the United States, the Secretary's Advisory Committee on Human Research Protections has published guidance on the rationales that may be used to justify the second key precondition; trial impracticability[44]:

> Appropriate ethical or scientific rationales might include, for example: (i) scientific validity would be compromised if consent were required because it would introduce bias to the sample selection; or (ii) subjects' behaviors or responses would be altered, such that study conclusions would be biased; or (iii)

Table 3. Three Examples of Trials Granted an Alteration or Waiver of Written Informed Consent

1. Dexamethasone for Cardiac Surgery Trial	
Design	Individually randomized controlled trial (2,800 patients)[24]
Trial objective	To determine whether high-dose dexamethasone reduces postoperative complications and prolongs hospital stay after cardiac surgery.
Method of consent	Altered consent (opt-out) used in standard of care arm only. Consent obtained in the nonstandard of care arm.
Medicinal products	Dexamethasone, placebo
Investigator's rational for altered consent	• In similar trials conducted in this population that have used traditional consent, rates of enrolment were less than 5% of hospitalized patients. Traditional consent would thus jeopardize the trial's ability to demonstrate real-world effectiveness. • There is a likelihood of patient anxiety and distress with the consent process. • Consent was only altered for patients receiving standard of care. Patients might be negatively affected by the knowledge that their physician does not know which treatment is best (damage to the doctor-patient relationship). • The patient recruitment phase of a trial utilizes a substantial portion of a trial's budget. The use of opt-out consent in this vanguard trial demonstrated that altered consent facilitated a high proportion of eligible patient enrolments (overall consent rate 98.5%) with a fivefold faster enrolment than usual for similar trials in this population. Trial costs were more than halved.
2. Supplemental Oxygen and Surgical Site Infection	
Design	Single site alternating cluster trial (5,749 patients)[3]
Trial objective	To test the hypothesis that supplemental oxygen reduces the risk of surgical site infection.
Method of consent	Waiver of consent
Medicinal product	30% or 80% inspired oxygen
Investigator's rational for waiver of consent	• The protocol-directed oxygen levels were routinely used at the site and the risks of supplemental oxygen were considered to be minimal. • Patients would not normally have a choice outside the trial (various oxygen concentrations used in routine care without patient discussion). • Clinicians were allowed to override protocol directed oxygen concentrations if they believed it necessary. • Previous small studies addressing this question had been inconclusive so a large study was required to provide definitive results. The costs associated with traditional consent would have made this local quality improvement study impracticable.
3. Bathing to Eliminate Infection Trial (ABATE)	
Design	53-hospital cluster-randomized (≈600,000 patients)[13]
Trial objective	To evaluate the impact of decolonization on multi-drug resistant organisms and hospital-associated infections in the general patient population outside intensive care units.
Method of consent	Waiver of consent
Medicinal products	Chlorohexidine, mupirocin
Investigator's rational for waiver of consent	• Hospital committees and leadership normally determine infection prevention policies, standardized nursing procedures, as well as the selection of drugs on hospital formularies rather than individual patients or practitioners. • Patients can always refuse a bath; protocol requires discontinuation if subjects show sensitivity to chlorhexidine. • Formal consent is impracticable; infection prevention requires a unified population-based approach which would be compromised if the intervention were substantially limited. Both the intervention and validity of results are dependent on the application system-wide. Comparative effectiveness research requires systems to be functioning similar to usual operations; consent may create bias due to lack of representative sample. • Outcomes are infectious and population-based approaches can yield different results than nonpopulation-based approaches.

> the consent procedure would itself create additional threats to privacy that would otherwise not exist; or (iv) there is risk of inflicting significant psychological, social or other harm by contacting individuals or families. Once the IRB has determined that the waiver or alteration does not adversely impact the ethical nature or scientific rigor of the research, logistical issues (e.g., cost, convenience, speed) may be considered.

Although this wording is not present in the revised Common Rule, it provides useful clarification on the types of rationales that may make a trial impracticable. It also highlights that not all justifications provided for our trials may fully meet the "impracticability" test. For example, the discomfort generated when doctors tell patients that they do not know what treatments are best is unlikely to make a trial impracticable. While this rationale alone may not meet the legal precondition for alteration or waiver, it may well support an ethics committee's overall assessment of the balance of risks, burdens, and benefits.

Use of Cost as a Rationale for Impracticability

One important question for pragmatic trials is whether "cost" can be used as a primary reason to justify a trial's impracticability. This debate is articulated by Gelinas *et al.*,[45] McKinney *et al.*,[18] and by Kim[46] who writes:

> Some may argue that informed consent is so fundamental that it should always be the default so that some modest or even moderate use of resources should always be accepted. Others may argue that if it can be established that a full informed consent is not necessary ethically, then it makes no sense to require it and expend unnecessary resources.

Considering the size of the three trials we present (especially Trial 3), all may have been prohibitively expensive without

Table 4. Determining Trial Risk

Country	Publication	Extract from National Policy/Guidance
United States	Department of Health and Human Services 45 Code of Federal Regulations 46. 111 (2)	"In evaluating risks and benefits, the IRB [Institutional Review Board] should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research)."
England	Medicines and Healthcare products Regulatory Agency: Joint Project Risk-adapted Approaches to the Management of Clinical Trials Involving Investigational Medicinal Products.	"Within a particular clinical trial, these [risks] can be categorized in relation to how much is known about the medicine(s) being investigated. These potential risks should be assessed relative to the standard of care for the relevant clinical condition and the level of clinical experience with the intervention rather than the patients' underlying illness or the *recognised* adverse effects of the intervention. The potential risks should be balanced against the level of risk that a trial participant would be exposed to outside of the trial."
Australia	National Health and Medical Research Council: National Statement on Ethical Conduct in Human Research 2007 (Updated 2018)	"In health research involving an intervention, the risks of an intervention should be evaluated by researchers and reviewers in the context of the risks of the health condition and the treatment or treatment options that would otherwise be provided as part of usual care."

alteration or waiver of consent. Gelinas *et al.* support the inclusion of cost as a justification for impracticability and take the position that research that infringes participant rights may be justified if, *the gravity of the rights infringement is minor and outweighed by the expected social value of the research*. Kalkman *et al.* also conclude that publicly funded investigator-led trials with high social value may have a stronger claim of "impracticability" than trials supported by commercial companies as investigator-led trials are less likely to have the resources to overcome these impracticability issues.[47] The group also propose a means for ethics committees to judge a trial's social value by defining its determinants: (1) the extent to which the research question has real world relevance; (2) the trial design's ability to generate a real world answer; and (3) the probability of direct uptake of the results by decision-makers in practice.[48]

Although incurring some expense to obtain consent is not by itself considered a justification for impracticability, some privacy laws do permit excessive cost to be used as a primary justification for waiver of consent to process data for observational research; including data relating to genetic material.[49,50] One could argue that in some cases, the risks posed by the disclosure of data may be no less than the risks posed by randomization in minimal risk trials. If ethics committees can take into account excessive cost when waiving consent for observational research but not for clinical trials, the disparity would seem a double standard. As articulated by Zeps *et al.*, in times of major economic rationalization of healthcare services, the use of valuable resources required to obtain individual consent could in itself be seen as unethical.[51]

Discussion

Most pragmatic trials are feasible without alteration or waiver of consent, especially if the consent process is simplified and investigators craft concise and readable documents.[52,53] But, in specific situations, it may be necessary to depart from traditional consent, leading to tensions between the rights of individuals and the needs of society that ethics committees must reconcile (fig. 1).

Balancing Risks and Benefits

For every trial, investigators and ethics committees must assess the potential risks and benefits of trial participation. But the risks and benefits to individual participants are not the only consideration. The consequences of trial participation for individuals should be balanced against the risks of unstudied health care to both current and future patients. Those seeking altered or waived consent often point to a pragmatic trial's high social value to justify the use of these models. For pragmatic trials comparing routine therapies, where the incremental risk of physical harm is established as minimal, the risk determination focuses on the potential for psychologic harm arising from infringements of a patient's right to autonomous choice. If a trial's high social value is used to justify the use of these models, an ethics committee will need to be reassured that its social value adequately counterbalances its potential harms.[54] So how should a trial's social value be quantified? Based on the determinants developed by Kalkman *et al.*,[48] we propose that social value can be considered as the ability of the trial to generate real-world evidence that has substantial potential to improve care or reduce healthcare costs, and a high probability of uptake by decision-makers.

However, even when an ethics committee deems an alteration or waiver ethically defensible, policy frameworks should ensure that those decisions are made transparently and accountably.

Maintaining Public Trust

The potential loss of public trust in the health system from widespread and uncontrolled nondisclosure of trial entry is a valid argument for limiting the use of alteration and waiver of consent. If patients no longer support research

Fig. 1. Balancing ethical requirements.

due to a loss of trust, this in itself may impact patients' welfare. As discussed earlier, Kim and Miller also caution that patient welfare is not only impacted by safety considerations such as the risks of the intervention, but also by the removal of a person's ability to make decisions based on their expectations and perspectives. Thus, the degree to which a patient would be expected to have preferences about the various treatment options is a key welfare consideration. Kim rightly warns that ethics committees should not treat all trials involving standard of care interventions as a "monolithic category of special ethical status" and that patients' reasonable expectations should be considered.[41,46]

Avoiding Scope Creep

Although the wider use of these models brings with it a greater risk of uncontrolled use of alteration or waiver; lessons can be learned from the use of waiver of consent for the processing of data for observational research. This is well established and sanctioned by law in many countries and proceeds under conditions which are transparent and tightly controlled to avoid scope creep. The open publication of information on all trials granted an alteration or waiver would provide the public with assurance that the rules around the use of these models continue to be strictly observed.

Engaging the Public

For all countries, particularly those without a current framework for altered or waived trial consent, increased public engagement to improve trial awareness and acceptance will not only enable consumers to join the debate, it will help create a "reasonable expectation" for the use of data for research and the use of randomization to make some quality improvement activities more robust. Notably, different communities will have differing levels of trust and any campaign should carefully consider how to engage communities that are especially distrustful of research or the medical establishment and also how best to build that trust.[55] As advocated by Kass *et al.*, more information about the views of informed and engaged consumers is needed.[56] Recent studies are already providing useful insights[56–60] indicating that generally, patients wish to be informed that they are entering a study, but are also accepting of consent models that reduce autonomy—especially when socially valuable research would be impracticable without their use.[61] The development of infrastructure to support increased levels of consumer involvement in research means investigators can now partner with consumers to coproduce their trials. This in itself will enhance our understanding of whether consumers and their communities are prepared to tolerate reduced autonomy.[62,63]

Rudimentary Framework

Ethics committees should be provided with tools to effectively manage the need to uphold basic ethical principles without unnecessarily impeding socially valuable research. A clear research-specific framework that describes a range of consent models would be a prerequisite for their wider acceptance. For countries that permit altered and waived consent, we summarize the key considerations from this review (table 5). A set of preconditions for alteration or waiver, derived from ethical guidelines or policy frameworks, guide the ethical and regulatory acceptability of these consent models—although their use in countries outside this review will be subject to the requirements of local policy frameworks.

Conclusions

The number of large-scale pragmatic trials adopting flexible approaches to informed consent is increasing. Most experts agree that healthcare systems that wish to embed pragmatic trials need to adopt consent models that more closely parallel those used in routine clinical practice. Most also agree that in some circumstances, altered or waived consent is ethically defensible, but the extent to which these models should be used is still widely debated. This discordance is reflected in international policy frameworks and key ethical guidance.

Of the three countries studied, the policy frameworks in the United States best support pragmatic trials. These frameworks are harmonized and permit altered and waived consent when certain preconditions are met. Importantly, these frameworks are research-specific and sanctioned by law. Not only does this provide investigators with the unequivocal assurance that altered or waived consent is legal, it also supports efforts to improve public acceptance of

Table 5. Elements Required for Altered or Waived Consent

Key Preconditions for Altered/Waived Consent

Before permitting altered or waived consent, an ethics committee must be satisfied that:

1. involvement in the research carries no more than minimal risk to participants;
2. the research is impracticable[1] without the use of the alteration/waiver of consent;
3. the potential benefits[2] of the research justify any risks of harm caused by the alteration/waiver of consent; and
4. the alteration/waiver will not materially affect the rights or welfare of the participants.
5. Whenever appropriate:
   - the proposed consent model is developed/ratified through consumer involvement
   - information about the prospective trial is broadcast to allow patients to exercise autonomy
   - participants are provided with additional pertinent information after participation.

[1]Impracticability may result from methodological issues or logistical issues. Examples of trial impracticability include:

a) scientific validity would be compromised if consent were required because it would introduce bias to the sample selection; or
b) participants' behaviors or responses would be altered, such that study conclusions would be biased; or
c) the consent procedure would itself create additional threats to privacy that would otherwise not exist; or
d) there is risk of inflicting significant psychological, social or other harm by contacting individuals or families or as a result of seeking consent.

[2]The assessment of a trial's potential benefits should include its social value which can be defined as: *the ability of the trial to generate real-world evidence that has substantial potential to improve care or reduce healthcare costs and a high probability of uptake by decision-makers.*

Further Considerations

1. General Points

- If the ethics committee establishes that traditional consent is not necessary ethically, logistical issues such as excessive cost may be used as a justification for impracticability if a trial's social value is deemed to substantially outweigh its risks and burdens.
- An ethics committee may deem it appropriate to selectively grant alteration or waiver for individual arms of a trial rather than the whole trial.
- For cluster trials, additional elements in '*The Ottawa Statement on the ethical design and conduct of cluster randomized trials*' should be considered.

2. Points relating to the components of informed consent

Consent to disclose trial participation

Consider whether nondisclosure of randomization will materially affect the rights or welfare of participants:

- Are all the treatments routinely offered to patients outside the trial setting and considered by the medical community as the best available treatments for the trial population?
- Are there material differences between the treatment arms (such as in the type of side effect or differing levels of trial burden) that may be important to participants?
- Is there properly informed uncertainty about the relative merits of the interventions being tested (genuine clinical equipoise)?
- Would patients have had a choice outside the trial? If so, would it be feasible for clinicians to override "randomization" if they, or their patient felt an alternative was preferable?
- Have investigators considered how to respectfully manage the concerns of trial participants who are unhappy with the loss of autonomy when informed of the non-disclosure of trial entry?

Consent to treatment and the requirement for written, signed and dated consent

Consider whether the process and timing of consent to treatment could mirror what would be deemed appropriate if patients were receiving the same intervention outside the trial—noting that routine care consent may range from written consent for elective risk-entailing interventions through to tacit consent for some components of complex interventions or health service decisions.

Consent to process data

Consider the following:

- Is the proposal for waiver of consent to process data compliant with local privacy law?
- Are there adequate provisions to maintain privacy and confidentiality?
- Are appropriate mechanisms for transparency in place?

these consent models. In contrast, England appears to have the least supportive frameworks. If adopted post-Brexit, the European Union Clinical Trials Regulation[38] will regulate all medicinal product trials in England and will require prospective, written informed consent for all but a small subset of cluster trials. Such a strict approach highlights a marked contrast in the "current thinking" of the Food and Drug Administration and the European Medicines Agency. Although differing cultural norms are likely to underlie policy differences, the extent of discordance is surprising, particularly as both regions are founding members of the International Council for Harmonisation whose stated mission is to achieve greater consistency worldwide. Adjustments to the least supportive frameworks appear necessary to align with the prevailing views of the research community and would support international efforts to conduct large, collaborative pragmatic trials that are currently hampered by "regulatory inconsistency."

Pragmatic trials are also hampered by "regulatory uncertainty," particularly difficulties interpreting the preconditions for alteration and waiver of consent, which many cite as the reason for the considerable variation in ethics committee opinion. To support ongoing international efforts to provide clarity on this topic, we summarize key points into

a rudimentary framework, primarily to assist investigators in navigating the ethical and regulatory minefield that surrounds the use of these models and to facilitate discussions with their ethics committees. In countries that permit the use of altered or waived consent, we call for explicit and risk-proportionate guidance for these socially valuable trials.

Limitations

Our review of interlinking regulations, particularly privacy laws, is not comprehensive. It is, therefore, possible that factors we did not identify influence the approaches to waiver in our countries and may also explain why certain legislation appears especially conservative. Trial activities such as the collection of tissue, trigger consideration for other laws not discussed herein. Although our analysis was reviewed by legal experts, none of the authors is a lawyer, much less with special training in this relatively arcane regulatory area. Our summary of relevant law is brief and thus necessarily omits detail and nuance. Our framework is rudimentary, but we hope it will contribute to international efforts to improve the environment in which pragmatic comparative effectiveness trials are conducted.

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Competing Interests

The authors declare no competing interests.

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