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# Ethics of Informed Consent for Pragmatic Trials with New Interventions

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ABSTRACT

**Objectives**: Pragmatic trials evaluate the comparative benefits, risks, and burdens of health care interventions in real-world conditions. Such studies are now recognized as valuable to the perimarketing stage of drug development and evaluation, with early pragmatic trials (EPTs) being explored as a means to generate real-world evidence at the time of regulatory market approval. In this article, we present an analysis of the ethical issues involved in informed consent for EPTs, in light of the generally recognized concern that traditional ethical rules governing randomized clinical trials, such as lengthy informed consent procedures, could threaten the "real world" nature of such trials. Specifically, we examine to what extent modifications (waivers or alterations) to regulatory consent for EPTs would be ethical. **Methods**: We first identify broadly accepted necessary conditions for modifications of informed consent (namely, the research involves no more than minimal risk of harm, the research is impracticable with regulatory consent, and the alternative to regulatory consent does not violate legitimate patient expectations) and then apply those criteria to the premarket and early postmarket contexts. **Results and Conclusions**: The analysis shows that neither waivers nor alterations of regulatory consent for premarket EPTs will be ethically permissible. For postmarket EPTs with newly approved interventions, waivers of consent will be ethically problematic, but some studies might be conducted in an ethical manner with alterations to regulatory consent.

***Keywords:*** comparative effectiveness, informed consent, pragmatic trials, real-world evidence.



Pragmatic clinical trials are randomized controlled trials (RCTs) that compare treatments in routine or "real-world" health care settings to inform clinical decision making [1,2] and are designed in such a way that real-world conditions are minimally interfered with [3,4]. Thus, real-world designs typically aim to recruit a high number of patients attending clinics while minimizing disturbance to routine clinical workflow.

Many commentators have noted, however, that there may be a tension between the goals of pragmatic RCTs and the traditional ethical rules governing RCTs. One challenge is the traditional regulatory informed consent process (which we refer to as "regulatory consent" [5]), which typically requires lengthy consent forms and procedures, which significantly alter the routine workflow of "real-world" clinical settings and therefore compromise the pragmatic nature of the trial [6–10]. Therefore, some have argued that in some types of pragmatic RCTs where the risks are very low and patient expectations are not violated, the regulatory procedures for obtaining informed consent could be altered [6,8] or even waived [11,12].

Pragmatic trials are typically associated with standard-of-care comparisons, and yet their value is not limited to treatments already used in clinical practice. Early pragmatic trials (EPTs) comparing new interventions with existing standards could generate real-world effectiveness data that can be valuable to health care decision makers even at the time of regulatory approval. Currently, the Innovative Medicines Initiative's
(IMI) GetReal consortium—consisting of over 90 stakeholders from academia, industry, and regulatory and reimbursement agencies—is exploring ways to facilitate the design and conduct of EPTs to bridge the "efficacy–effectiveness gap" [13]. In this context, EPTs can study unapproved treatments in the premarket phase (premarket EPTs) as well as newly approved treatments in the *early* postmarket phase (postmarket EPTs). Recently, the *New England Journal of Medicine* published results from the first premarket pragmatic phase IIIb comparative effectiveness trial, designed by the pharmaceutical company GlaxoSmithKline in the field of chronic obstructive pulmonary disease [14].

Traditionally, pragmatic trials have not been attractive to commercial sponsors: There is considerable business risk associated with failure to prove comparative effectiveness and high

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trial costs [15,16]. And since pragmatic trial evidence is not required by regulators for market access or explicitly required by reimbursement agencies, sponsors do not have any incentive to design and conduct pragmatic trials. However, this landscape seems to be changing.

There is growing interest, at least in Europe, in providing early pharmacoeconomic evidence to open up formularies for insurance coverage and to justify higher charges for novel interventions. In Germany, the Institute for Quality and Efficiency in Health Care, which oversees the national drug reimbursement policies for one of the largest markets in Europe, has expressed a clear preference for head-to-head trials with appropriate comparators and almost always rejects indirect comparisons as evidence [17]. Furthermore, in many European countries, restricted reimbursement is given pending the outcome of postmarketing research. This, nevertheless, requires a process that may take a significant amount of time (months to even years) [18]. Thus, EPTs that allow for direct, real-world comparisons hold the potential to bridge the efficacy–effectiveness gap and to reduce the time it takes for patients to gain access to new and effective drugs [19]. Although EPTs are still relatively rare, they may become more frequent in the future.

In determining the opportunities and ethical constraints of advancing EPTs, the tension between key pragmatic features and the regulatory requirements of research ethics plays a central role. This article explores the possibilities of introducing more pragmatism in premarket (phase III) and postmarket (early phase IV) clinical trials by analyzing the ethical issues surrounding informed consent for such trials. This analysis of informed consent is crucial because informed consent is based on the principle of respect, one of the central principles of research ethics, and the requirements of this principle cannot be met by merely considering the risk–benefit ratio [5]. Specifically, we consider whether modifications to traditional informed consent (which we refer to as "regulatory consent") would be ethical. We first identify broadly accepted necessary conditions for modifications (waivers and alterations) of informed consent and then apply those criteria to the EPT context. We analyze the issue for both premarket EPTs and postmarket EPTs and, importantly, also distinguish between the permissibility of alterations (e.g., simplified consent) and that of full waivers. We conclude that that there are salient differences between pragmatic trials, especially between premarket EPTs and pragmatic trials with standard-of-care treatments, and delineate their implications for the obligation to seek informed consent from trial participants.

## A Framework for Analyzing the Ethics of Informed Consent for EPTs

As noted, the increased interest in standard-of-care pragmatic trials has led the research community to debate if and how traditional regulatory consent can be ethically modified—either waived entirely or altered in some way so that the goals of pragmatic trials can be achieved without violating ethical norms [6–8,12]. Indeed, some changes in certain research regulations explicitly accommodate "simplified" procedures for obtaining consent for some types of pragmatic clinical trials. The recent amendments to the European Union (EU) Clinical Trials Directive state that a special subset of cluster randomized trials (i.e., those testing drugs registered and used in accordance with their marketing license, or of equivalently low research risks) may make use of "simplified means" to obtain informed consent [20]. It is notable that these provisions seem to envision trials that involve low research risks with a consent process that preserves transparency about the research by using simplified means, in this case an "opt out" procedure for consent.

In the United States, for studies that assess drugs that are used in conformity with their market license (therefore not subject to the U.S. Food and Drug Administration [FDA] regulations) some modification to regulatory consent may be allowed if the following criteria are met: 1) The research involves minimal risk; 2) the science would be impracticable with regulatory consent; and 3) the rights and welfare of the subjects are not violated [21]. There are valid reasons to interpret the last condition—that of not violating the rights and welfare of the subjects—as falling under a broader concept of not violating the reasonable expectations of the subjects [5]. Commentators in the literature [5,9,22,23] as well as EU and US regulations [20,21,24] broadly track the same conditions for modifications to regulatory consent procedures in clinical trials (again, unless FDA regulations come into play). Thus, we use these conditions to assess the current expansion of standard-of-care pragmatic trials to EPTs by examining how they play out for earlier stages in the research and development of new interventions.

## Necessary Conditions for Modifications of Informed Consent

### *Minimal Risk*

One uniformly accepted necessary condition for altering or waiving regulatory consent is that the research risks of the trial be minimal. However, the exact method to determine whether a study has only minimal research risks is still being debated. Some commentators have argued that randomized trials comparing the effectiveness of two treatment options that fall within the standard of care do not pose more than minimal risks compared with their use in clinical practice [25,26]. Others have pointed out that such a broad definition ignores the significant range of research risks involved in clinical trials that compare "standard-of-care" practices [27]. Faden et al. [12] imply that a pragmatic trial can be deemed to pose minimal risk if "[t]here are few differences between the [regulatory approved] drugs in how they are administered, frequency of administration, or side-effect profiles" and "both drugs are well tolerated by patients and adverse events are rare."

Recently, a more systematic and formal approach to analyzing the research risks of standard-of-care pragmatic trials has been proposed [28]. This approach shows that the research risks in standard-of-care pragmatic trials are minimal when one or both of the following conditions are met: 1) The *ex ante* estimates of risks and benefits of the treatments to be compared in the trial are similar; and/or 2) the allocation ratios of treatments inside and outside the trial are similar. Since EPTs (premarket or postmarket) compare one or more treatments that are not already widely in use, the second condition cannot be met for such trials. Therefore, for the purposes of this article, the framework shows that an EPT can be considered to pose minimal risk only if the treatments being compared can be regarded as having similar *ex ante* risk–benefit profiles (Table 1).

### *Impracticability*

Another necessary condition for modification of informed consent is that the trial would be impracticable if regulatory consent were required [7,22,29]. Impracticability need not strictly mean that one cannot conduct a study *at all* without a waiver or alteration of regulatory consent (e.g., some deception studies are impossible if subjects are aware of being in the study) but also that the study's goal is unlikely to be achieved. In the case of pragmatic RCTs, "impracticability" will most likely refer to the latter. In this regard, commentators have pointed to specific

**Table 1 – Criteria to assess the acceptability of consent modifications for early pragmatic trials (EPTs).**

| Criteria | Definitions | Premarket EPT (phase III) | Postmarket EPT (phase IV) |
|---|---|---|---|
| **Is the study a minimal-risk study?** | Are the two (standard-of-care) treatments generally regarded as having similar *ex ante* risk–benefit profiles? | No. Since no independent review by a regulatory authority has been performed, more than minimal risk in face of uncertainty seems a more reasonable view (risks and benefits of compared treatments cannot be assumed to be similar). | Maybe. It depends on the data available. The new drug could be seen as having a better risk–benefit profile, or it could be seen as more risky because of lack of market experience. Will require case-by-case judgment. |
| **Is the study impracticable with regulatory consent?** | *Cause:* Is the loss of data quality caused by selection bias or inability to recruit a sufficient number of patients and can this loss be reasonably attributed to regulatory consent? | Will require case-by-case judgment. It will be important to establish that the quality loss is caused by extrinsic effects of regulatory consent. | Will require case-by-case judgment. It will be important to establish that the quality loss is caused by extrinsic effects of regulatory consent. |
| | *Effect:* Is the expected loss of data quality so extreme that the trial is not worth performing? | Will require case-by-case judgment. | Will require case-by-case judgment. |
| | *Alternative*: Apart from modifying regulatory consent, are there no available means or resources that may be reasonably expected to counter the loss of data quality? | Maybe. Although the majority of premarket EPTs is industry sponsored, indicating some sort of availability of resources to enhance recruitment without compromising too much on real-world conditions. | Maybe. Although most postmarket EPTs will still be industry driven, increasing the likelihood of resolving data-quality issues with resources. |
| **Does waiving or altering regulatory consent respect patient expectations?** | Does waiving or altering regulatory consent respect any legitimate expectations patients may have of having a say in whether tested treatments are received inside the trial versus outside the trial or to be informed about how treatment allocation occurs? | No. The test intervention remains "experimental" when it concerns novel, unapproved treatments, regardless of explanatory or pragmatic designs. Thus, patients always have legitimate reasons to expect to be informed about all trial and intervention aspects and to decide whether to participate. | Maybe. Treatments are no longer "experimental," since they are accepted—i.e., on the market but presumably not yet in widespread use. Patients have a reasonable expectation of being informed about relatively new treatments in a trial and in what ways the compared treatments differ in terms of side-effects, use, and so on. Will thus require case-by-case judgment. |
| **Overall assessment** | • Are all three conditions likely to be met?<br>• Is a waiver of regulatory consent ever justified?<br>• Are alterations to regulatory consent ever justified? | • No premarket EPT will meet all three criteria.<br>• No premarket EPT can be conducted with a waiver of consent.<br>• No premarket EPT can be conducted with alterations to regulatory consent. | • Some postmarket EPTs could to some extent meet all three conditions.<br>• No postmarket EPT can be conducted with a full waiver of informed consent.<br>• Some postmarket EPTs may be conducted with altered, simplified informed consent. |

challenges of regulatory consent pertaining to low recruitment rates [30] and selection bias, as well as to lack of generalizability to real-world settings because of the mandated use of nonroutine (i.e., not part of the routine workflow of a clinic) procedures associated with regulatory consent [2,6,31]. The primary threats to this particular type of impracticability relate to what we will label "data quality," that is, the extent to which the data allow drawing of reliable conclusions about the real-world effects of the tested interventions. Obviously, this kind of impracticability is a matter of degree and needs to be balanced against other relevant factors; some loss of generalizability might be tolerable, for instance. To determine whether true impracticability exists, we propose that three questions be asked (Table 1).

The first question "Is the loss of data quality caused by selection bias or inability to recruit a sufficient number of patients, and can this loss be reasonably attributed to regulatory consent?" aims to clarify the cause of the expected loss of quality of trial results. It is important to assess the reasons behind the selective or low recruitment. Such reasons can be either intrinsic or extrinsic to the purpose of informed consent. For example, patients who are content with their current therapy and do not want to jeopardize their disease control have reasons to refuse enrolment. Such refusals are intrinsic to the purpose of informed consent. Attempts to deviate from regulatory consent—for example, a waiver of consent—to enhance recruitment in such cases defeats the very point of informed consent and violates the ethical mandate to give prospective participants the opportunity to make such decisions.

Sometimes, however, patients are not enrolled for reasons that are extrinsic to the purpose of informed consent. Suppose patients are not approached by physicians because of time constraints (or the nurses in the clinic are also too busy, and

recruitment of patients for studies is not part of their routine workflow) or patients refuse enrolment because of the unexpected inconvenience of the informed consent process [32]. If the reasons for patients not enrolling in a pragmatic trial are extrinsic to the purpose of informed consent, there is a legitimate argument of impracticability—which, in turn, might allow for modifications of regulatory consent (if other conditions are met).

The next question "Is the expected loss of data quality so extreme that the trial is not worth doing?" then assesses the extent of the effect. This question carries, by far, the most weight for the impracticability assessment and requires further explanation. If regulatory consent leads to a selection of unrepresentative patients or substantial biases in the data, the trial will not be worthwhile. The claim that a particular pragmatic trial is impracticable because of regulatory consent issues will need to be substantiated, nevertheless, since some degrees of selection might not be problematic. For example, if it is unlikely that the consent procedure will significantly modify the treatment response, matching the consent for research to the way the consent for a treatment is obtained in the real world might not be strictly necessary to ensure high generalizability [33]. Researchers may apply for a waiver of informed consent because they anticipate that informed consent will make the trial scientifically invalid and, thus, impracticable [34]. However, such *a priori* speculations do not always turn out to be true, as illustrated by the fact that there are practical instances where investigators learn that informed consent does not preclude the generation of scientifically valid results [35,36]. Although it is impossible to specify ahead of time what empirical evidence to rely on (given the many parameters of particular research protocols), ethics committees should demand rigorous data-based justifications from investigators.

The third question "Apart from modifying regulatory consent, are there no means or resources available that may be reasonably expected to counter the loss of data quality?" explores alternatives. There are two approaches to this problem: 1) More efforts, such as reimbursing physicians for time spent on consent procedures, contracting study nurses to obtain informed consent, or providing incentives to patients to compensate them for the inconveniences they may experience during the trial, are directed to recruitment procedures; or 2) regulatory consent is altered or waived.

### *Patients' Expectations*

A third condition that is generally believed to be necessary to justify modifications to the regulatory consent procedure is ensuring that patients' rights and interests are not violated [8,9,22]. However, whether bypassing informed consent for a randomized trial constitutes an infringement of patients' rights is still being debated [22]. With regard to some pragmatic trials with standard-of-care interventions, it has been argued that if the risks are minimal and there are no *a priori* meaningful differences between the compared treatments, a waiver of prospective consent might be defensible for some pragmatic trials that "have no or only minor effects on important patient interests" [10] or, in a somewhat different description, when careful review indicates that there is "no plausible reason to conclude that patients are likely to have meaningful preferences for one intervention over another and/or that patients would object to the overall purpose of the study" [12].

The obligation to respect the legitimate expectations patients may have with regard to the care they receive is grounded in the principle of respect for persons [5]. The expectation criterion is necessary because in some studies, even in the absence of quantitative differences in risk of harm in the aggregate [28], patients may, in fact, have a meaningful reason for preferring one treatment over another, since there may be some qualitative differences between the two interventions being compared and this may make the choice a classic "preference-sensitive" decision [27]. For example, two treatments may be thought to have comparable magnitude of side effects but the nature of these side effects may be different (e.g., mild itch vs mild constipation); or one treatment may have greater potential for efficacy but also greater potential for adverse effects compared with the alternative; or one treatment may have greater magnitude of effect but perhaps with a lower probability compared with another treatment that has potentially higher probability of helping a person but with lower magnitude of effect. Patients typically expect to have a say in such preference-sensitive decisions. In practice, many pragmatic trials will be interested in comparing interventions to see if, for example, treatment A is, indeed, more efficacious despite being more burdensome compared with treatment B. In such cases, one can assume that patients would value having at least the option to actively choose a specific treatment (based on their own specific preferences) and decline random treatment allocation. The increasingly acknowledged model of shared decision making incorporates the value of patient preferences and trust [37]. In cases where meaningful treatment preferences may exist, full waivers of informed consent may thus compromise the valuable goals of shared decision making, although altered, yet transparent, consent procedures may not. Finally, even when there may not be a strong preference-sensitive choice at issue (because no qualitative differences or potential risk–benefit trade-offs exist between the compared treatments), patients may still have legitimate expectations with regard to enrolment in a trial and how their data are being used. Current empirical evidence shows that the general public has expectations regarding informed consent even for low-risk pragmatic trials [38].

## Application of the Criteria to the Case of EPTs

Our criteria—derived from broadly accepted necessary conditions for modifications of informed consent—provide a basis for deliberating on the different justifications for modifying regulatory consent requirements for pragmatic clinical trials in general *and* for exposing the differences between premarket EPTs and postmarket EPTs in comparison with pragmatic trials investigating standard-of-care treatments. Table 1 provides answers to some questions—for example, whether each condition, in general terms, is likely to be met by premarket EPTs and postmarket EPTs—and demonstrates how these features affect the permissibility of either waivers or alterations of regulatory informed consent.

### *Can Some EPTs Be Minimal-Risk Trials?*

In assessing whether a trial involves minimal risk, there is a clear distinction between EPTs conducted in the premarket phase and those conducted in the period directly following regulatory market approval. It seems unlikely that any premarket EPT can be classified as a minimal-risk trial. The experimental treatment is not an accepted treatment in terms of widespread use in practice or having received regulatory approval. Regulatory approval for market access is more than a mere stamp of approval. It indicates that rigorous, independent review has taken place to validate the findings from pivotal phase III trials on safety and efficacy. In the face of uncertainty, it is difficult to overturn the presumption that premarket EPTs may pose more than minimal risk. This presumption is, of course, built into the regulatory system. All regulatory agencies that oversee market approvals generally do not even recognize the category of

minimal risk for RCTs that fall under their jurisdiction and also do not have provisions for allowing any modifications to regulatory consent [20,21,24,39,40].

In the case of postmarket EPTs, all compared interventions are "accepted" and "standard-of-care" treatments, in the sense that any qualified professional may employ them. However, it is also true that the novel intervention will have relatively little data compared with the older interventions, especially longer-term safety data. Even if the new drug could be considered to have a better risk–benefit profile (after all, this is the common goal in the development of a new treatment), there will still be limited real-world experience regarding its long-term effects or rare adverse events. For example, the sale of the antidepressant nefazodone was discontinued after several years because postmarketing studies had shown that the drug caused severe liver toxicity in rare incidences [41]. Thus, for postmarket EPTs, some considerations need to be examined on a case-by-case basis. These considerations may include availability of data on the long-term outcomes, benefits, and harms of the treatment under study compared with those of other currently available therapies and provider experience.

### *Are EPTs Impracticable If Regulatory Consent Is Required?*

The three questions we recommend for assessing the impracticability of pragmatic trials need to be answered on a case-by-case basis. The tension between data quality of a "real-world" pragmatic trial and the requirement of regulatory consent will arise whether or not the RCT is comparing standard-of-care treatments or new treatments. However, the availability of means to counter the loss of data quality that may accompany full regulatory consent may depend on the sponsor and the purpose of the trial.

The Salford Lung Study—sponsored by the UK pharmaceutical company GlaxoSmithKline—directed great efforts into inclusive enrolment of patients in a premarket EPT. Although the study report does not mention specific challenges related to informed consent [14], a preliminary commentary published earlier by the investigators while the study was still ongoing does suggest that regulatory informed consent posed substantial operational challenges but that the strategies to counter these effects were not believed to compromise the quality of the results [42]. The publicly sponsored postmarket eLung and Retropro pragmatic trials also experienced substantial recruitment challenges and faced much more difficulty in overcoming them [30]. Physicians interviewed by the study team stated that they perceived time to be the biggest barrier to patient recruitment and that money could be used to "create" more time [30]. These examples show that there may be situations where the impracticability is something that can be overcome with sufficient resources to support the regulatory consent procedures without fatally compromising the real-world nature of the trial. In such cases, one would need to consider how much society (or a company) would be willing to pay to obtain answers to a specific pragmatic question. In cases where economic resources alone cannot eradicate recruitment problems resulting from regulatory consent procedures in a particular pragmatic trial, one would need to examine whether the social value of the trial would justify alterations to regulatory consent.

Such resource-dependent impracticability implies that a large pragmatic trial representing the goals of a so-called "learning health care system" [9] may have a stronger claim of "impracticability" than a one-off industry-funded pragmatic trial. The notion of a learning health care system entails conducting continuous comparative effectiveness research at low public cost in routine care settings to directly improve clinical decision making. The requirement to direct large amounts of resources to overcoming operational hurdles in every pragmatic trial may lead to an overburdened and clogged up health care system. Commercial sponsors of one-off EPTs, however, would be incentivized to conduct such trials for business reasons (e.g., to obtain insurance coverage) and would also more likely have the financial means that could, to some extent, mitigate the impracticability barrier. Of course, this does not rule out the possibility that some EPTs would be impracticable without some modifications to regulatory consent, but such a determination needs to be made on a case-by-case basis. Our point is simply that the impracticability condition may be more difficult to meet for EPTs compared with standard-of-care RCTs conducted in a learning health care system.

### *What Kinds of Patient Expectations Are Relevant in EPTs?*

In premarket EPTs, the test intervention is "experimental," since, by definition, it has not been accepted yet for use in the real world, regardless of explanatory or pragmatic designs. It seems obvious to say that patients always have legitimate reasons to want to be fully informed about a trial on experimental treatments.

In the early postmarket phase, the compared treatments are no longer strictly experimental but accepted treatments in terms of regulatory approval. Nevertheless, when comparing postmarket EPTs with pragmatic standard-of-care trials, more uncertainty exists with newly marketed interventions because of less experience and data. However, there may be existing data (e.g., data used to obtain marketing approval) suggesting that the new intervention has a better risk–benefit profile compared with current standard treatments. Thus, this could be considered a classic "preference sensitive" situation (the new treatment may be better but less is known about it); patients' preferences and expectations should be expected to be highly relevant in such situations.

It appears that in postmarket EPTs, patients have a reasonable expectation of being informed—thus precluding entire waivers of consent—about new treatments in a trial and in what ways the compared treatments differ in terms of side effects and use. However, the test intervention, although new, is effectively accepted for use in clinical practice. As such, it may not violate patients' expectations to forgo the kind of extensive disclosure of all the risks and benefits related to the new drug's use as in a typical clinical trial. Instead—as an example of an alteration to regulatory consent—*some* postmarket EPTs may be allowed to compare interventions by using a simpler consent process that mimics the course of everyday clinical practice [8]. This is not the same as saying that when clinicians fail to obtain ethically valid informed consent in a clinical setting, the research consent process can be modified to mimic this subpar consent. Quite the contrary, for in situations where the status quo is inadequate, the simplified research consent would have the effect of raising the "real world" clinical consent to an ethically acceptable level.

## Implications for Informed Consent in EPTs

We have shown that that there are salient differences in terms of risk and patient expectations between pragmatic trials, especially between premarket EPTs and pragmatic trials with standard-of-care treatments. In the case of premarket EPTs, it is clear that from an ethical point of view, modified consent will not meet the "minimal risk" condition or the "patient expectation" condition. Our analysis thus shows that no premarket EPT will qualify for a waiver of regulatory consent and that any suggestion to alter regulatory consent before market approval should be scrutinized with extreme care (Table 1).

In the case of postmarket EPTs, it seems clear that a complete waiver of consent would also not be permissible. Although it is possible that in rare instances such trials may qualify as minimal-risk trials, the generally available resources (a brief modified consent process may allow pragmatic goals to be achieved with little extra resources [8]) and patients' legitimate expectations to at least be informed that their (potentially new) treatment is being chosen randomly (e.g., to inform reimbursement decisions) rules against bypassing informed consent altogether. There is a possibility that some postmarket EPTs could be ethically conducted with an altered regulatory consent process. However, such an alteration would only be permissible if the impracticability condition were strong—that is, the compromise on data quality resulting from regulatory consent requirements is significant enough that the trial's value is threatened, even with significant resources.

We would like to point out that we have put aside the question of what exactly the alterations to regulatory consent look like; for the purpose of this article, we have confined our efforts to assessing whether it would be ethically acceptable to consider alterations at all. We also stress that our analysis does not indicate that there is no place for pragmatic trials in the earlier stages of a drug's life cycle—quite the contrary. In general, at whatever stage, making the results of clinical trials more applicable to real-world practice is crucial to evidence-based clinical decision making. And, indeed, regulatory informed consent procedures for clinical trials rarely resemble the verbal discussion patients and their physicians have when deciding on a new treatment. Nevertheless, we have demonstrated that the more novel the intervention that a pragmatic trial evaluates, the harder it is to argue for ethically modifying regulatory consent procedures. There are many other ways to increase the pragmatic nature of phase III and early phase IV clinical trials: Applying broader participant inclusion criteria, limiting trial procedures that are disruptive to routine care conditions, and including research sites that are more representative of real-world practice are just a few examples of how this can be done and which thus merit further investigation.

## Conclusions

From a public health perspective, pragmatic clinical trials that yield information early on about the comparative benefits, risks, and burdens of health care interventions can be valuable in guiding practice and policy. Although EPTs have traditionally not been attractive to commercial sponsors, there is a trend among European reimbursement agencies to increasingly require more "real-world" data about new interventions in comparison with existing standards. We analyzed how the often-debated tension between the requirement for regulatory consent and the enabling of standard-of-care pragmatic trials affects our thinking about the acceptability of modifications (waivers or alterations) of the regulatory consent procedure in premarket and postmarket EPTs.

If, as it is often claimed, full regulatory consent would make EPTs impracticable to conduct, then would some EPTs be permissible with modifications to regulatory consent? Our analysis reveals the following points: 1) No premarket EPT can be conducted with either a waiver of or an alteration to regulatory consent; 2) although no postmarket EPT can be conducted with a waiver of regulatory consent, some may be conducted ethically with an alteration to the regulatory procedure; and 3) thinking about EPTs can help further pinpoint morally relevant issues in pragmatic trials across the different stages of a drug's life cycle.

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