HHS Public Access

Author manuscript

Am J Bioeth. Author manuscript; available in PMC 2024 August 01.

Published in final edited form as:

Am J Bioeth. 2023 August ; 23(8): 10–21. doi:10.1080/15265161.2022.2063435.

Think pragmatically: investigators' obligations to patient-subjects when research is embedded in care

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Abstract

Growing interest in embedded research approaches—where research is incorporated into clinical care—has spurred numerous studies to generate knowledge relevant to the real-world needs of patients and other stakeholders. However, it also has presented ethical challenges. An emerging challenge is how to understand the nature and extent of investigators' obligations to patient-subjects. Prior scholarship on investigator duties has generally been grounded upon the premise that research and clinical care are distinct activities, bearing distinct duties. Yet this premise—and its corresponding implications—are challenged when research and clinical care are deliberately integrated. After presenting three case studies from recent pragmatic clinical trials, we identify six differences between explanatory trials and embedded research that limit the application of existing scholarship for ascertaining investigator duties. We suggest that these limitations indicate a need to account for the implications of usual care and to move beyond a narrow focus on the investigator-subject dyad, one that better reflects the team- and institution-based nature of contemporary health systems.

Introduction

Traditional explanatory research—which seeks to evaluate interventions under ideal conditions—has acknowledged shortcomings, and there is growing interest in novel research methods that deliberately embed research into the delivery of clinical care, such as pragmatic clinical trials (PCTs). PCTs are designed to evaluate interventions under real-world conditions and thus commonly take place where patients are already receiving their care. They are designed to be flexible along dimensions such as eligibility and recruitment and are often conducted with alterations or waivers of regulatory consent (Kim and Miller 2016; Morain and Largent 2021). A growing body of literature highlights the challenges associated with pragmatic research (Califf and Sugarman 2015; Kass et al. 2013; Faden et al. 2013; Largent, Joffe, and Miller 2011; Morain and Kass 2016). A through-line of that literature is that traditional ethical and regulatory paradigms, designed with explanatory research in mind, are often ill-suited for oversight of research embedded in care (Kass et al.

2013; Largent, Miller, and Joffe 2013). Traditionally, clinical research and clinical care have been considered distinct activities governed by distinct normative commitments. Integration of research into care, therefore, challenges the norms of both.

These challenges are clear in the context of the relationship between investigators and subjects. Investigators conducting traditional explanatory research are understood to have moral obligations to their subjects; these obligations are particularly well defined when the investigator is at the bedside, and the subjects are also patients (Joffe and Miller 2008). Yet investigators in PCTs often conduct their research at a substantial remove from the bedside, shaping and evaluating patient care in ways subjects may not explicitly consent to or even be aware of. What are investigators' duties to subjects when research is embedded into the delivery of clinical care? And how, if at all, does the alteration or waiver of informed consent for research interventions change investigators' duties to research subjects?

Our goal here is three-fold. First, we present case examples, drawn from actual PCTs, to illustrate questions regarding the nature and scope of investigator duties that can arise in embedded research. Our examples surface challenges regarding obligations to share information with potential clinical relevance that is generated from embedded studies, but we suggest they reflect broader challenges in enumerating investigators' moral obligations. Second, we argue that existing scholarship regarding the nature of investigator duties in explanatory research offers limited guidance for embedded research due to key differences between the two approaches. We conclude with recommendations for future scholarship to support the ethical conduct of research embedded in care.

Case Studies

The following three case studies illustrate the challenge of assessing the nature and scope of investigators' duties to patient-subjects in embedded health research. In each case, the research team learned things about the care of individual patients that led them to ask what they should do. Patients could reasonably be expected to want to know of this information, but these same patients were also unaware that research was being conducted. Members of the research teams sought to understand whether their respective studies could even go forward or, alternatively, if they had any obligation to share information of potential clinical relevance with patient-subjects.

Case Study 1: Untreated atrial fibrillation

IMplementation of an RCT to imProve Treatment With Oral AntiCoagulanTs in Patients with Atrial Fibrillation (IMPACT-Afib) was a randomized PCT that explored whether an educational intervention targeted at patients with atrial fibrillation (i.e., an abnormal heart rhythm) and their clinicians could reduce underuse of oral anticoagulants (the recommended treatment for atrial fibrillation) and, in turn, prevent avoidable strokes (Sabin et al. 2019; NCT03259373). The investigators identified approximately 80,000 eligible patients using health care claims data. These patients had a known diagnosis of atrial fibrillation, but claims data did not indicate that they were receiving anticoagulants. It was, however, possible that some were receiving anticoagulants despite the lack of documentation. The investigators' plan was to randomize eligible patients either to the control arm for usual

care or to the intervention arm, in which patients and their clinicians would receive information about the potential benefits of anticoagulation for atrial fibrillation. The control group faced no new risks, and the educational intervention was low risk; moreover, the absence of evidence regarding the educational intervention's beneficial effect on care meant the control group was not being deprived of a known benefit (Sabin et al. 2019). The investigators sought a waiver of regulatory consent because—consistent with the conditions for alteration or wavier outlined in the Common Rule*—consent would make the research impracticable and could introduce bias by informing patients in the control group about the study's objective. The research team did not anticipate difficulty securing institutional review board (IRB) approval; however, the U.S. Food and Drug Administration (FDA), a project funder, expressed concern as to the ethical acceptability of the study design given the substantial risk of stroke associated with untreated atrial fibrillation. While undertreatment with anticoagulants was a known issue across the participating health systems—and in clinical practice more broadly— the design of the trial would identify *specific* individuals who, claims data suggested, were not receiving recommended treatment to prevent avoidable strokes. In the words of the project oversight committee: "[I]f care may be suboptimal and the researchers are in a position to do something about it, shouldn't they intervene and not simply study it?" (Sabin et al. 2019)

Case Study 2: Untreated osteoporosis

The Lumbar Imaging with Reporting of Epidemiology (LIRE) trial was a stepped-wedge PCT involving over 250,000 patient-subjects across four large health systems. The trial examined the effect of adding prevalence data for common findings in people *without* back pain into spine-imaging reports on health care utilization, specifically on spine-related interventions and opioid use (Jarvik et al. 2020). The study was conducted with a waiver of regulatory consent, as the intervention was implemented at the clinic level, making consent infeasible (NIH Collaboratory Coordinating Center Ethics & Regulatory Core 2013). After the LIRE trial was completed, the research team conducted a planned secondary analysis of their data to explore heterogeneity of treatment effect. During this secondary analysis, the team identified several thousand individuals for whom imaging findings indicated possible osteoporosis but for whom there was no documentation in the electronic health record (EHR) indicating that a diagnosis of osteoporosis had been communicated to the patient or that treatment for osteoporosis had been initiated. The research team sought guidance from the Ethics and Regulatory Core of the NIH Collaboratory, which provides consultation on and develops best practices for the conduct of PCTs, regarding the ethical obligations related to the identification and management of these osteoporosis findings (NIH Collaboratory Coordinating Center n.d.).

*The Federal Policy for the Protection of Human Subjects or Common Rule lists five criteria that research proposing a waiver or alteration must conform to: (1) the research involves no more than minimal risk to subjects; (2) the research could not practicably be carried out without a waiver or alteration; (3) the research could not practicably be done with de-identified private information; (4) subjects' rights and welfare will not be adversely affected; and (5) whenever appropriate, the researchers will provide subjects or their legally authorized representatives with information after participation (45 CFR §46.116).

Case Study 3: Poor emergency medical care

The third case comes from a PCT, conducted with a waiver of informed consent, which examined how EHRs might be used to improve screening for child abuse. While reviewing EHRs during the trial, the research team identified multiple instances of "poor medical care." For example, a neonate presenting in the emergency department for an injury also had a full-body rash, a fever, and a mother with a known herpes infection. According to the investigators, the child's symptoms in combination with the mother's health history should have triggered an evaluation for herpes, which has substantial risk for severe illness or death among neonates (Rudnick and Hoekzema 2002). Yet, no such evaluation was recorded in the EHR. In a second example, a child with an animal bite received sutures, which are contraindicated for animal bites due to increased risk of infection. In discussions with one of us, the principal investigator contemplated whether there was a duty in any of these cases to notify the patient's family, the treating clinician, or the health system about potential shortcomings in the patient's emergency medical care.

Limitations of Relying on Explanatory Research Ethics

There is, as yet, little agreement about the nature of investigators' duties to patient-subjects in embedded PCTs. The absence of agreement is exemplified by recent scholarship on the identification and management of collateral findings in PCTs—that is, individual-level findings from PCTs (discovered intentionally or unintentionally) that may have implications for health, but which were not generated to address the trial's primary research question(s) (Morain, Weinfurt, et al. 2020; Morain, Mathews, et al. 2020; Bollinger et al. 2020). At least initially, collateral findings appear analogous to incidental findings arising in the context of explanatory research—that is, "finding[s] concerning an individual research participant that [have] potential health or reproductive importance and [are] discovered in the course of conducting research but is beyond the aims of the study." (Wolf et al. 2008; Illes et al. 2006) Yet, on closer examination, the analogy proves inapt, and it is clear that prior guidance on incidental findings can offer only limited guidance for collateral findings (Morain, Weinfurt, et al. 2020).

Here, using the example of incidental and collateral findings, we show that the literature on investigators' obligations to subjects in explanatory research cannot simply be extended to embedded research. We begin by briefly reviewing prominent conceptions of the investigator-subject relationship, which have been used to derive what is owed to subjects in explanatory research. We then identify six relevant differences between explanatory and embedded research that render these existing models insufficient to derive what investigators owe to subjects in embedded research.

Obligations to Subjects in Explanatory Research

In explanatory research, investigators' duties to subjects are generally understood to be distinct from physicians' duties to patients. The defining feature of the physician-patient relationship is the "overriding commitment of the physician to that individual patient's benefit." (Brody and Miller 2013) As described by Churchill, "[m]uch of the privilege afforded to physicians, in terms of access to the patient's body and personal life, is

legitimated by the singularity of purpose with which physicians have claimed the well-being of their patients as their goal." (Churchill 1980) The investigator can claim neither this singular focus on the patient-subject's wellbeing nor the moral authority that accompanies it (Churchill 1980). While investigators often hope the study intervention will benefit subjects, this is not their primary aim. Rather, their primary aim is to conduct high-quality research yielding generalizable knowledge for the benefit of future patients (Brody and Miller 2013; Litton and Miller 2010). In light of their respective purposes, physicians' duties are best understood as *fiduciary*, while investigators' duties are best understood as *protective* (Litton and Miller 2010). Investigators ought to protect subjects from harm or exploitation experienced as a result of the research (Litton and Miller 2010).

Among the most prominent conceptions of investigator-subject relationships is the partial entrustment model (PEM). Introduced by Richardson and Belsky, the PEM addresses investigators' ancillary care obligations; ancillary care is medical care subjects need but that goes beyond what is required to conduct the science safely or to redress research-related injuries (Belsky and Richardson 2004). According to the PEM, subjects partially entrust investigators with their welfare by permitting them access to private aspects of their bodies, including data and specimens. (The entrustment is *partial* because subjects do not fully entrust their medical welfare to an investigator, as would a patient to a clinician (Wolf 2013)). Investigators assume corresponding duties (Richardson and Cho 2012). According to the PEM, the *scope* of investigators' duties to subjects is defined by those aspects of the subject's health which come to light "in the course of conducting research." (Richardson 2008; Richardson and Cho 2012) By taking medical histories, conducting physical exams, ordering scans, or administering drugs, investigators assume duties of care related to the information obtained through those procedures (Richardson 2008). The *strength* of those duties is then determined by a combined five considerations: (1) vulnerability, or how much difference getting care would make to the individual's welfare; (2) dependence, understood as how reliant the individual is on the research team for care; (3) engagement, representing the intensity or duration of a relationship between the individual and the investigator; (4) gratitude, intended to reference any debt the investigator may owe the individual for willingness to undergo risky, painful, or inconvenient procedures; and (5) cost, encompassing consideration of the countervailing costs to the research enterprise for providing care (Richardson 2008). Since its introduction, the PEM has been extended to address incidental findings in clinical research, and, more recently, incidental findings in secondary research using biobanks—a context which shares ethically relevant parallels to at least some PCTs, given the potential lack of any direct interaction between investigator and subjects (and potentially also even a lack of any awareness of the research by the latter) (Richardson 2008; Richardson and Cho 2012; Morain, Weinfurt, et al. 2020; Richardson and Cho 2020).

An alternative approach to investigator-subject relationships was proposed by Miller, Mello, and Joffe in an influential 2008 article. They argued that, while investigators do not have a fiduciary relationship to research subjects, they nevertheless have contracted into a professional relationship—one in which the investigator is given privileged access to private information with the subject's consent. This creates a limited obligation for investigators to provide assistance regarding findings outside the scope of the contractual professional

obligation (Miller, Mello, and Joffe 2008). The challenge for investigators, Miller and colleagues argue, is to balance the need to "fulfill obligations of beneficence, as it is understood in the research context, while not going so far as to contribute to the therapeutic misconception," or otherwise promote unreasonable expectations about the purpose of research (Miller, Mello, and Joffe 2008). They note that their analysis largely converges with that of the PEM (Miller, Mello, and Joffe 2008).

These two influential models have been used extensively to guide decision-making about incidental findings arising in explanatory research (Morreim 2018). However, the models become strained when applied to collateral findings arising from embedded research. There are (at least) six differences between explanatory and embedded research contexts that expose the limitations of extending existing models from the former to the latter.

Difference 1: Embedded research is often conducted with a waiver of regulatory consent.

As just noted, recommendations regarding the management of incidental findings in explanatory research have heavily emphasized the role of informed consent. Take, for example, the work by Miller and colleagues, described above. Their argument assumes both that the parties entered the research relationship consensually and that the parties understand the goal of the research to be the generation of generalizable knowledge. Yet, as our three case studies illustrate, in many PCTs and other embedded research studies, though investigators have access to private information, their research is conducted with a waiver of regulatory consent. Consequently, neither of Miller and colleagues' assumptions hold in this context. Even if the research is conducted with an alteration of regulatory consent, rather than a waiver, the assumptions seem tenuous. Importantly, an alteration or waiver of consent does not necessarily mean that investigators have no obligations to address collateral findings. As Richardson and Cho note in their extension of the PEM to collateral findings in biobanking, obligations cannot be waived merely because data were obtained without "morally required permission" (Richardson and Cho 2020). However, if investigators do have obligations to patient-subjects in embedded research, they cannot be grounded in subjects' grant of regulatory consent.

Difference 2: Embedded research may not involve direct communication between patient-subjects and investigators.

Accounts of investigators' obligations to disclose incidental findings in explanatory research generally assume that investigators will disclose incidental findings directly to the subject, with whom they have a relationship rooted in consent. In embedded research, investigators will often be unable to contact or may even be prohibited from contacting subjects. This makes a certain amount of sense. Consider receiving a call from an unfamiliar investigator —perhaps affiliated with a different institution than the one at which you receive your clinical care—who informs you that you may have osteoporosis. Patients—who may not know that they are or have been research subjects—might find it off-putting (at minimum) to learn information that may have substantial implications for their health or medical decision making from someone wholly unknown to them. Clayton has called this the problem of the "cold call" (Clayton 2008). Waivers and alterations of regulatory consent can be ethically justified, and many people find them acceptable once they understand the tradeoffs involved

(Morain and Largent 2021). Yet learning through a cold call that one has been a research subject may undermine trust in the research enterprise.

In response to these types of challenges, Richardson and Cho suggest that no direct investigator-subject communication is necessary: "[j]ust as one can return a library book by putting it in the post, so too can one return a finding by asking … [an] intermediary to recontact the contributor." (Richardson and Cho 2012) Theirs is not a unique position. Whicher and Wu have similarly argued that investigators may "disclose collateral findings to the hospital, health system, payer, or clinical staff" rather than directly to subjects (Whicher and Wu 2020). It would then be the obligation of the party who receives word of the collateral finding to act upon it. Unfortunately, qualitative research suggests an absence of shared agreement among relevant embedded research stakeholders about who should be responsible for information about collateral findings (Morain, Mathews, et al. 2020). This raises a legitimate concern that *no one* will assume responsibility. Thus, approaches to disclosure that rely on intermediaries, while reasonable on their face, seem susceptible to the challenges made apparent by a childhood game of 'telephone.' The message may become garbled, or the chain of communication may abruptly end.

If investigators cannot disclose collateral findings directly to subjects and cannot reliably trust in intermediaries to relay this information, one might ask if investigators have a duty to disclose such findings to subjects at all. If ought implies can, it may be that investigators' duty in embedded research is simply notifying an appropriate intermediary. Yet, if this is the case, we must appeal to unique features of embedded research as compared to explanatory research to understand why the duty is formulated this way.

Difference 3: Addressing individual-level findings in embedded research entails costs for institutions and the research enterprise.

A third limitation of existing theories of investigator duties is their incomplete consideration of downstream implications particularly relevant to embedded research. For example, cost is among the five criteria identified by the PEM for assessing the strength of investigator duties. According to Richardson, "[a] rough way to estimate the degree to which incurring monetary costs will frustrate scientific goals is to assess that cost relative to the relevant research budget." (Richardson 2007) In considering the potential cost implications in the PCT context, Richardson and Cho suggest that—as data for research are already linked or easily linked to patient identities—recontact will be logistically and financially manageable (Richardson and Cho 2020). There is, however, reason to be skeptical of this claim. For at least some embedded PCTs, the scale of the research may plausibly require contact of many thousands of individuals across multiple health systems. Think of the 80,000 eligible individuals identified by the IMPACT-Afib research team: to contact all those individuals, postage alone could run over $45,000. This is not an insignificant expense in the context of most study budgets.

Yet, even if we were to accept these notification costs as reasonable (and also to accept the opportunity costs of foregone research or other valued activities), there are at least two additional concerns relevant to embedded research. The first such concern is that costs are not simply restricted to the costs of recontact and disclosure. Consider, for example,

the LIRE trial. After patient-subjects are notified, additional relevant costs might include resources needed to corroborate the research findings, such as additional clinical visits and testing for osteoporosis, as well as subsequent medical management for thousands of patients. There may also be costs associated with litigation, if, for instance, patients were to interpret the investigators' disclosure as an indication of malpractice by their treating clinician (Morain, Mathews, et al. 2020). Imagine that the neonate who apparently was not evaluated for herpes infection in Case Study 3 ultimately died of such an infection and that the parents subsequently learned of the treating clinicians' oversight from investigators. Surely, they would consider litigation. Even if litigation was unlikely to succeed (a fact-specific determination), there would be financial and emotional costs to clinicians and possibly to their employers associated with defending against such claims. Certainly, investigators do not view their research budgets as capable of absorbing costs related to downstream medical management or litigation; nor should they be required to absorb them (Morain, Mathews, et al. 2020). Some may argue—and we would agree—that it is inappropriate to count these as costs for purposes of determining investigators' obligations to patient-subjects. If patients really need care, their clinicians should provide it, and their insurers should cover it. As appropriate, the medical malpractice system should compensate patients injured by their clinician's negligence.

Yet, even if we assume that expenses related to collateral findings can and will be covered by the appropriate parties, we must confront a second, closely related concern. The relevant costs of addressing collateral findings are not merely tallied in dollars and cents, nor are they necessarily restricted to a single study. To a greater extent than in explanatory research, embedded research requires that investigators form strong partnerships with institutions, such as hospitals and health systems, to succeed (Larson et al. 2016; Weinfurt et al. 2017). Furthermore, institutional participation in embedded research is entirely voluntary. If disclosure of collateral findings to patient-subjects (who may, as the case studies illustrate, number in the thousands) was to undermine institutional willingness to participate in research—whether due to health care costs, fear of litigation, or other concerns—investigators' future ability to conduct socially valuable embedded research may be limited. In recent empirical work exploring investigators' attitudes and experiences with LIRE-type cases, several investigators described such concerns. They characterized decision-making about their obligations as involving the weighing of not only the implications for their current research, but also the implications for their future research activities (Morain, Mathews, et al. 2020).

Here, critics may reasonably reply that institutions should not punish investigators or withdraw their support for embedded research because research reveals deficiencies in care; or, perhaps, critics might argue that upstanding investigators should conduct their research elsewhere if they face institutional barriers to doing what is right. While this might be ideal, we have repeatedly heard from investigators that undermining of relationships is a serious concern for PCTs (Morain, Mathews, et al. 2020). This concern must be appreciated in the context of critiques that existing structures already disincentivize institutional participation in PCTs, thereby exacerbating the substantial unmet need for trials addressing societal, public health, or community needs (Platt, Simon, and Hernandez 2021). At minimum, therefore, an account of investigators' obligations in embedded research requires

acknowledging the consequences of disclosing information beyond the cost implications for a single study.

Difference 4: Embedded research occurs in real-world settings, where gaps in care are common.

A fourth limitation in trying to infer investigators' duties to subjects in embedded research from accounts of investigators' duties in explanatory research is how these accounts understand subjects' dependence or otherwise vulnerable status. According to the PEM, the criterion of dependence involves an assessment of the extent to which relevant medical or technological capabilities are otherwise available to subjects, or if they are available in a given area (Richardson 2007).

In the three case studies presented above, we can reasonably assume that there are numerous providers within the relevant health systems or in the surrounding vicinity who have the knowledge, abilities, and resources to manage atrial fibrillation, osteoporosis, and animal bites in accordance with clinical practice guidelines. This would suggest that patient-subjects' dependence on investigators in embedded research is often limited and, by extension, that they have a weak claim on investigators to disclose collateral findings. Yet, the fact that capable providers are available may have little bearing on whether the individual will, in fact, receive the right diagnosis or correct clinical management without action by the research team. Notably, studies like IMPACT-Afib are socially valuable because we know that patients routinely *do not* receive indicated care, and investigators are looking for ways to remedy the known gap between clinical practice guidelines and real-world clinical practice. This gap may be more pronounced for underserved populations, who face significant barriers regarding the availability, affordability, and approachability of health care services and routinely confront disparities. Consequently, some scholars have argued that researchers may have greater duties to aid low-resource patient-subjects in PCTs (Stewart et al. 2020). Given the kinds of questions that embedded research seeks to answer and its emphasis on real-world settings, we may need a new, more capacious understanding of dependence for embedded research.

Furthermore, emerging empirical evidence indicates that patients and members of the public *want* to be notified of collateral findings (Bollinger et al. 2020; Weinfurt et al. 2021). They value this information due to its clinical actionability (when it is clinically actionable), but they also value it due to its import for future decision-making, including whether to seek care from a different provider or health system going forward. The animal bite example is illustrative: though we hope the child is once bitten, twice shy, the parents may reasonably wish to choose a different emergency department if the need again arises. While these preferences are not themselves determinative of investigators' duties, they further challenge the concept of dependence as understood in explanatory research contexts.

Difference 5: Individual-level findings in embedded research may have implications for the well-being of non-subjects.

A fifth limitation encountered when extrapolating duties from explanatory research to embedded research relates to the former's general lack of consideration for non-subjects.

In explanatory research, we tend to assume that a research study is a closed system. Because the aim of explanatory research is to see if an intervention works under idealized circumstances, investigators typically work within clearly delimited conditions. The use of strict inclusion and exclusion criteria for enrollment and identification of a finite study population means the population of individuals to whom an investigator might owe a duty is typically well defined.

Given the protective relationship between the investigator and subject and also the closed system of research, it is understandable that accounts of investigators' duties focus on duties to those *enrolled* in research. Yet, because PCTs are typically embedded in the delivery of care, ensuring their ethical conduct may require more than protecting the rights and welfare of those who meet the regulatory definition of a "human subject." For instance, it may be necessary to consider those individuals who might not be the targets of the study and from whom no data is collected, but who might nevertheless be affected by their exposure to the study intervention (Smalley et al. 2015). Furthermore, the nature of questions explored in embedded research may make these studies more likely to surface findings with clinical relevance not only to individual subjects, but also to other patients. Consider a paradigmatic example of an incidental finding in explanatory research: an investigator conducting research involving brain imaging identifies a possible brain tumor in a healthy subject's scan (Miller, Mello, and Joffe 2008). Such a finding is understandably of great import to the subject, but it is unlikely to signal anything about the potential medical needs of others. Contrast this with the LIRE case. If the LIRE data suggest that care is inconsistent with clinical guidelines for osteoporosis within the study's sample of spinal-imaging patients, there is a reasonable expectation that other patients in the participating health systems are experiencing similar shortfalls in their care. A focus solely on investigators' duties to patient-subjects, as currently framed in the existing literature, appears insufficient in assessing the nature or scope of duties to non-subjects.

Difference 6: Clarity on how to address individual-level findings is often lacking in embedded research.

The sixth limitation of applying existing guidance on investigators' duties in explanatory trials to the context of embedded research is that existing guidance focuses on how investigators ought to proceed when they are confronted with one individual's health care needs. Take a classic case: imagine that investigators conducting a study of vaginal microbicides happen to identify a subject's extrauterine pregnancy, which is deemed unrelated to the microbicide; provision of care to address that extrauterine pregnancy would be ethically appropriate, and providing that care would not undermine the study (Participants in the 2006 Georgetown University Workshop on the Ancillary-Care Obligations of Medical Researchers Working in Developing Countries 2008). Yet, it is rarely so straightforward in embedded research. Collateral findings often reflect gaps between best practice and actual practice; moreover, the need to find effective means of closing these gaps is among the key motivations for employing embedded research approaches.

In some embedded research, like IMPACT-AFib, identification of individuals who are not receiving indicated treatment is inextricably linked to the research aims. Underuse of

anticoagulants is a known problem, and the IMPACT-AFib research team was not sure at the outset if an educational intervention would significantly increase prescribing. (NB: It did not.) Thus, randomizing participants to receive either usual care or the educational intervention was a scientifically and methodologically robust approach. Previously, it has been argued that the IMPACT-Afib research team had no *a priori* obligations to the patient-subjects (Morain 2019). Yet, once the trial began, there was a feeling that the team had assumed *some* obligations to patient-subjects, though their nature and scope proved controversial (Morain 2019; Largent 2019). Among other reasons, it was not clear how investigators could or should address the problem they had identified. Means of recourse available in explanatory trials were unavailable to them: they could not prescribe anticoagulants to patient-subjects themselves, for example, or refer them to a different provider. An effective means of increasing anticoagulant prescribing for patients across a health system has yet to be identified—otherwise, the study would not have been necessary. Requiring that the investigators' deliver the educational intervention to everyone at the outset would have led to a less rigorous research design, reducing the study's value. Intervening without studying the educational intervention was an option, albeit an unattractive one, given the need for evidence-based solutions.

In LIRE, because the collateral findings of osteoporosis arose in a secondary analysis, there were no questions of whether the trial should go forward or if it should be redesigned. Nor were there concerns that addressing these findings would negatively affect the study. But, in LIRE as in IMPACT-AFib, it was not clear *how* the investigators might address the findings. Underdiagnosis and undertreatment are well documented in the osteoporosis literature (P. D. Miller 2016). Whereas the appropriate treatment for one subject's extrauterine pregnancy is clear, the appropriate means of resolving systemic inadequacies in osteoporosis care are not. Given known shortcomings in translation and implementation of evidence-based guidelines into clinical care, it is critical to examine what responsibilities investigators and other stakeholders have to patient-subjects when embedded research deliberately finds or unintentionally illuminates widespread deficits in patient care.

Toward An Account of Investigator Duties in Embedded Research Ethics

Given the limitations outlined above, we do not think that it is possible to understand investigators' duties to patient-subjects in embedded research by reasoning from their duties in explanatory research. The nature and scope of those duties must be understood as distinct in this context. A successful account of investigators' obligations in embedded research should resolve questions regarding collateral findings and also advance our understanding of other aspects of the investigator-subject relationship. Although developing a full account of these duties is beyond the scope of this article, we offer one warning and two suggestions for a fruitful path forward.

Avoid A Fiduciary Framing

A potential response to the aforementioned limitations of existing accounts of investigator duties would be conclude that the duties of investigators to subjects in the context of embedded research should be fiduciary, akin to those of physicians. On the one hand, this

is understandable, particularly for trials with waivers of regulatory consent, because subjects are likely to conceive of themselves solely as patients, with corresponding expectations for how they will be treated by their clinicians and the broader health system in which they seek care. It would also be consistent with a longstanding and prominent tendency to view the ethics of clinical relationship through the therapeutic lens of the patient-physician relationship (Litton and Miller 2010).

Nevertheless, even in embedded research, the research-care distinction retains value (Largent, Miller, and Joffe 2013). To quote Litton and Miller, "the significant social value of producing generalizable knowledge provides strong reason to consider physician-researchers' duties differently" than those of physicians to patients (Litton and Miller 2010). Therefore, we should continue to reject the view that investigators' duties are equivalent to those of physicians. This is especially true as such a view could, taken to the extreme, lead to the conclusion that—in cases such as IMPACT-Afib where there is a known gap in care—health systems should simply implement promising interventions, rather than systematically studying them. While undoubtedly well-intentioned, such an approach would undermine the primary aim of embedded research: to generate socially valuable research to advance the quality and efficiency of health care, and ultimately, to improve health.

Account for the Shortcomings of Usual Care

Prior research ethics scholarship has typically focused on the risks and burdens introduced by a subject's participation in explanatory research—a paradigmatic example is the risk of taking an investigational new drug. But many of the risks and burdens that attract concern in embedded research are those associated with subjects' receipt of *usual*, rather than optimal, care. All three case studies reflect instances when investigators realized that subjects' care had apparently fallen short. Investigators repeatedly (and predictably) will identify these gaps when conducting embedded research.

The recognized shortcomings of usual care have implications for understanding investigators' duties well beyond collateral findings. For example, a review of qualitative scholarship with investigators and other key stakeholders involved in the conduct of embedded research reveals concern on the part of some stakeholders that randomizing some individuals to a placebo or control arm while others are randomized to receive an intervention aimed at remediating known gaps in care may "fail to provide them [individuals in the control arm] with potential benefits." (McLennan et al. 2018) Similar worries have arisen in discussions of the design of NIH-funded PCTs. This concern may be amplified when investigators are conducting research in settings and contexts where deficiencies in care are widespread and widely acknowledged—for instance, nursing homes that heavily rely on Medicaid often have fewer funds to devote to care, which may lead to lower quality of care for residents overall (Mor et al. 2011).

The challenge of defining investigators' obligations to subjects—particularly when investigators have identified potential shortcomings in usual care—will only accelerate with the growing use of data science and big data research. While some scholarship has begun to explore the tension between remedying problems and conducting research (Sabin et al.

2019; Morain 2019; Largent 2019), no formal guidance has emerged to advise investigators or institutions about these issues.

Look Beyond Investigator-Subject Dyads

In outlining the limitations above, we repeatedly saw that institutions occupy a distinctive role in embedded research. They are the site of research and care, and may serve as crucial gatekeepers, shaping investigators' access to patient-subjects (Whicher et al. 2015). This suggests that an account of obligations to subjects in embedded research needs to broaden its focus from the dyadic relationship between investigators and patient-subjects to a model that better reflects the team- and institution-based nature of both clinical care and embedded research in contemporary health systems (McKinney 2019). Investigators' duties might not always be to patient-subjects—or, they might be broader than to patient-subjects alone.

This implies that there is need for new paradigms of accountability encompassing other actors. Institutions are more fully partners in embedded research than they are in explanatory research. Consequently, they are an important party in assessments of what we owe to one another in the conduct of embedded pragmatic research. Investigators may have obligations to institutions, but institutions may also have novel obligations. For example, what do institutions owe to patient-subjects because they allow investigators to conducted embedded research? Further, we need an understanding of institutions' obligations both to *facilitate* or *conduct* embedded research to inform the effective delivery of high-quality clinical care services and systems, and also, importantly, to *implement* the findings of that research so as to effect meaningful change for patients (Faden et al. 2013; Largent, Joffe, and Miller 2011; Morain, Kass, and Faden 2018).

Opening the aperture to see more than the investigator-subject dyad offers the potential to mitigate some of the aforementioned limitations with respect to collateral findings specifically and in embedded research generally. For example, health systems who participate in embedded research might have an ethical obligation to disclose collateral findings to patient-subjects. Further, they might have an obligation to ensure that all patient-subjects have an opportunity to experience the potential benefits of a research intervention—for example, by asking investigators to consider a step-wedge or cross-over design. They might need to commit prospectively to implementing interventions that are shown to be effective or to consider the sustainability of any proposed intervention before entering into an agreement with investigators, somewhat akin to existing considerations for post-trial access in planning within traditional explanatory clinical trials. In this way, duties might be viewed as owed not only to patient-subjects in any given study but also to the broader patient population within the health system.

We acknowledge that looking beyond the investigator-subject dyad raises many questions. One might inquire, for example, whether duties are stronger for institutions that have made an explicit commitment to adopting a "learning health system"-type model—one that deliberately seeks to "drive the process of discovery as a natural outgrowth of patient care" and to in turn apply the results of that discovery to consistently improve the quality, safety, and value of care (Olsen, Aisner, and McGinnis 2007; Davis, Williams, and Stametz 2021)—than for those that have not. A related question is how to ensure that those institutions that

have adopted a “learning health system”-type model (and the patients and clinicians within them) are not unfairly burdened as they undertake the critical work of generating socially valuable knowledge. This is important given that participation in embedded research is, at this stage, voluntary. Additional questions surround the issue of how we might account for the persistent injustices in access to both clinical care and research that have systematically failed to allocate fairly the benefits and burdens of research. These are important issues, and we welcome further scholarship that explores these questions. Critical aspects of this scholarly inquiry include identifying the relevant trade-offs presented by alternative conceptions of institutional responsibilities (e.g., a higher standard for management of collateral findings in specific individuals may mean fewer resources to support other values, including future embedded research activities), and engaging with affected stakeholders in how to weigh these trade-offs. Ultimately, this scholarship should inform organizational policies related to the conduct of embedded research.

Conclusion

The growth of PCTs and other research activities that embed research into clinical care challenges traditional understandings, developed in the context of explanatory research, of what investigators owe to subjects. Our analysis illustrates the limitations of this traditional understanding for the management of collateral findings, but these limitations extend beyond the collateral findings context, and ultimately suggest the need for a new conception of duties in embedded research. A promising approach is to expand our focus to look not just on the investigator-subject dyad but also at the institutions where embedded research takes place. Future scholarship should explore the implications of this shift, and the corresponding implications for individuals, institutions, and populations.

Acknowledgements

We are grateful to the trial leaders and study team members of the three case studies for sharing valuable insights about their trials. We also thank the faculty and staff of the Baylor College of Medicine Center for Medical Ethics and Health Policy, who offered insightful feedback during a works-in-progress session on an earlier draft of this manuscript, as well as two anonymous peer reviewers.

Funding Statement:

This work was supported within the National Institutes of Health (NIH) Health Care Systems Research Collaboratory by the NIH Common Fund through cooperative agreement U24AT009676 from the Office of Strategic Coordination within the Office of the NIH Director. Supplemental funding for this work was provided by the National Center for Complementary and Integrative Health of the NIH under award number U24AT009676-02S2. This work was also supported by the National Institute on Aging (NIA) of the NIH under award number U54AG063546, which funds the NIA Imbedded Pragmatic Alzheimer’s Disease and AD-Related Dementias Clinical Trials Collaboratory (NIA IMPACT Collaboratory). Dr. Largent is also supported by the NIA under grant award number K01AG064123 and by a Greenwall Faculty Scholar Award. The views presented here are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

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