PRAGMATIC RANDOMIZED TRIALS WITH NEW INTERVENTIONS: AN ETHICAL ANALYSIS

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Pragmatic randomized trials with new interventions: an ethical analysis.
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Pragmatische gerandomiseerde studies met nieuwe interventies: Een ethische analyse

(met een samenvatting in het Nederlands)

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Prof. dr. D.E. Grobbee

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Dr. G.J.M.W. van Thiel

To my parents

MANUSCRIPTS ON WHICH THIS THESIS IS BASED

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Chapter 8: Kalkman S, van Thiel GJ, Grobbee DE, van Delden JJ. Responsible use of pragmatism in randomized trials with new medicines.

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CHAPTER 1

GENERAL INTRODUCTION

INTRODUCTION: THE CURRENT CLINICAL TRIALS ENTERPRISE

In the paradigm of evidence-based medicine, randomized controlled clinical trials (RCTs) are considered to provide the most reliable knowledge for informing both clinical and regulatory decision-making about the risks and benefits of biomedical interventions (1). Market authorization typically requires new interventions to be tested in RCTs with highly-selected, idealized patient populations using study protocols that ensure the highest chance of treatment response (2). Though so-called 'explanatory trials' are essential for generating reliable data on drug safety and efficacy, they have shown to poorly predict the actual, real world effectiveness of drugs as used in routine care settings by more heterogeneous patient populations (3). In addition, since explanatory trials aim to obtain scientific knowledge about the more isolated effects of pharmaceutical products, use of placebo is preferred. Once interventions have received regulatory approval for market access, there is very little incentive for drug companies to collect data on the real world benefits, risks and burdens of their products compared to existing standards. This means that for most drugs that are available on the market it is unknown whether they are more or less effective than existing standard of care treatments for the same condition. The lack of real world evidence on the comparative effectiveness of pharmaceutical interventions has led to a knowledge gap which has become known as the 'efficacy-effectiveness gap' (4).

The requirement of well-controlled conditions in RCTs stems from more than epistemic considerations only; to safeguard the rights and interests of human subjects participating in clinical research, a wealth of ethical guidelines and regulations equally dictate a certain level of scrutiny and control for RCTs (5). The observed mismatch between the requirements for clinical research and patient needs has sparked debate about whether the current clinical trials enterprise—and the rules and regulations governing it—is still apt to properly direct efforts towards protecting those who are most in need of protection while at the same time advancing improvements in day-to-day patient care. Following the HIV/AIDS epidemic in the 1980s, Carol Levine already commented that "the basic approach to the ethical conduct of research and approval of investigational drugs is one born in scandal and reared in protectionism" (6). Indeed, numerous scandals of unethical research conduct involving human subjects have fundamentally shaped research ethics guidance in the Western world (5).

Nowadays, a mounting challenge for regulatory authorities is to balance the need of preventing unsafe and inefficacious drugs from entering the market with that of providing patients timely access to the most effective treatments (7). Real world data collection and synthesis at the time of regulatory market approval is currently being explored as a means to bridge the efficacy-effectiveness gap (8). 'Real world evidence' indicates the evidence derived from data collected from observations among patients that are representative of the target population in routine care settings (9). One proposed strategy to generate real world evidence includes the use of pragmatic trial designs already in the process of drug development. Pragmatic randomized clinical trials or simply, 'pragmatic trials', is a term used to describe a range of RCTs comparing

the relative risks and benefits of different biomedical treatments in real world conditions with the aim of directly informing health care decision-makers (1, 10). Given the interest in so-called 'early' pragmatic trials to better address society's needs, ethical analysis is essential to help ensure that the results of designing such a new practice actually meet these needs and can be responsibly upheld in the long run.

EXPLANATORY AND PRAGMATIC ATTITUDES

Different stakeholders—such as patients, physicians, payers and policy-makers—benefit from answers to pragmatic questions of the type: does this treatment improve outcomes relevant to patients once applied in real world conditions (11)? The value of pragmatic trials thus lies in their ability to capture real world data with the scientific rigor of an RCT. Pragmatic (or real world) design features include, for example, eligibility criteria based on the characteristics of the population that will receive the treatment in clinical practice, recruitment and consent procedures that reflect routine care, minimal research protocol restrictions for physicians on how to prescribe treatments or how to follow-up patients and no formal plans to improve compliance of the test treatment (12).

The terms 'pragmatic' and 'explanatory' are characteristics that were assigned to clinical trials by French statisticians Daniel Schwarz and Joseph Lellouch in the 1960s (13). They set out from the observation that trialists often failed to identify and ethically justify the purpose and design of their RCTs. In their landmark paper, Schwarz and Lellouch made a distinction between explanatory RCTs, aimed at understanding the effects of a biomedical intervention under equalized and well-controlled conditions ('can it work under ideal conditions?') and pragmatic trials that address questions about the effectiveness of those interventions in practical settings ('does it work in real life?'). According to the authors, the research question should ultimately determine the type of approach required to answer the question. Schwarz and Lellouch explained that if the aim is to acquire information about the isolated effects of two compared treatments (i.e., to "give an answer to the scientific problem") the treatments will need to be compared under "idealized" or "optimized" conditions (13). This means that the intervention requires testing in a highly selected, responsive group of patients and that so-called extraneous factors will need to be eliminated to capture the difference in biological responses. In contrast, the pragmatic approach aims to compare interventions under the conditions as they would be applied in practice to answer the question: which of the treatments should one prefer? The pragmatic approach is driven by a practical question aimed at decision-making—rather than at solely acquiring scientific information—and therefore deliberately includes extraneous effects, such as the placebo effect, into the analysis (1).

Schwarz and Lellouch concluded that there is great discrepancy between trial designs and their intended purposes (mostly explanatory designs intended to answer pragmatic questions) and that this practice raises ethical concerns regarding the justification for the enrollment of research participants. They wrote: "In the first place, fundamental research aimed at the verification of a biological hypothesis is done on a relatively arbitrary population which is

ultimately treated as a means rather than an end; as such, the use of human subjects must be impermissible except in special cases. Normally, explanatory work must be done on animals, therapeutic trials on human subjects being limited to pragmatic experiments." (13) Schwarz and Lellouch did concede that some explanatory work can only be done on human research participants and that therefore explanatory trials may be ethically defensible in some cases. The authors did not provide any specific guidance on when to do so, yet they did propose to let ethical considerations dominate when deciding in what order explanatory and pragmatic trials should be conducted, depending on the valued objectives—immediate applicability of the knowledge versus "greater enlightenment" in the distant future.

THE RISE OF REAL WORLD EVIDENCE

Despite Schwarz and Lellouch's oft-cited paper, concerns remain that the way health care research is currently conducted is not apt to identify the care most appropriate for individual needs and conditions (14, 15). In both the United States (US) and Europe, different collaborative initiatives have been set up to understand what the challenges are that current health care systems face in translating research evidence into clinical practice. The Clinical Trials Transformation Initiative (CTTI), a public-private partnership established in the US, states that "[t]he clinical trials enterprise is in crisis. The complexity and cost of trials has resulted in a system that is unsustainable and often fails to provide patients and regulatory agencies with reliable and timely information about treatment and prevention options" (16). When looking particularly at clinical trials, different authors have recently pointed out that the extent to which trial results can be extrapolated, or generalized, to the actual population who will receive or undergo a biomedical intervention in 'real life' is highly limited (14, 17). A series of papers aptly titled 'Increasing value, reducing waste' published in the medical journal *The Lancet* in 2014 highlight the need for bringing back clinical or patient relevance into the clinical research enterprise (18).

In discussions on the topic, the terms 'pragmatic', 'naturalistic' and 'real world' are all used somewhat interchangeably to indicate the same type of trial approaches and conditions (19). Ideally, they refer to circumstances in which, among others, all patients who would be eligible for the treatment in practice would be eligible for enrollment in the study; physicians are allowed the same kind of flexibility in delivering the intervention as they are used to outside the study; patients are recruited in ways that resemble routine practice; and conditions in which patients are not encouraged to adhere to the intervention any differently than they would be outside the trial (12, 19). Typically, real world evidence tracks health outcomes that are clinically relevant or patient-centered. Such endpoints generally capture quality of life or treatment satisfaction rather than surrogate outcomes that substitute clinical endpoints (20).

The Innovative Medicines Initiative (IMI) supports the call for real world evidence and established the pan-European IMI GetReal consortium in 2013, engaging a variety of different stakeholders from academia (clinical epidemiology, biostatistics, research ethics), the pharmaceutical industry, health technology assessment (HTA) agencies (such as Zorginstituut Nederland and the National Institute for Health and Care Excellence, *NICE*), regulatory bodies

(such as the European Medicine Agency, *EMA*) and patient representatives to jointly work on strategies to implement real world evidence earlier into the process of drug development and evaluation (8). US counterparts are the National Patient-Centered Clinical Research Network (PCORnet) (21) and the National Institutes of Health (NIH) Collaboratory (22).

Particularly in the US, pragmatic trials are equated with RCTs that evaluate the comparative effectiveness of different approved or accepted, standard of care interventions in routine care settings. For example, the Active Bathing to Eliminate Infection randomized trial (ABATE) compares routine care bathing against bathing with chlorhexidine soap in non-critically ill, hospitalized patients to evaluate the comparative reduction in microbial infections (23). Another area of interest in the US is the comparison of two or more approved drug therapies, of which the example of a pragmatic trial evaluating two blood pressure lowering medications is probably the most paradigmatic (24). IMI GetReal focuses on real world evidence collection and synthesis in earlier stages, knowingly, around the time of regulatory market approval of the test interventions—indicating activity in early post-market research (phase IV) as well as late pre-market research (phase III). IMI GetReal is envisioning pragmatic trials in the like of the Salford Lung Study (SLS), which is the first and so far only pre-market pragmatic trial conducted. The SLS was designed by the pharmaceutical company GSK to complement the experimental drug's regulatory submission (encompassing required safety and efficacy data) with evidence on the drug's real world, comparative effectiveness (25, 26).

IMPLEMENTING PRAGMATISM IN CLINICAL TRIALS

Promoting pragmatism in clinical trials is of growing interest to a variety of stakeholders: patients have an interest in receiving timely access to effective and affordable drugs, clinicians require a sound evidence-base for their patient prescriptions, health policy-makers need to know what drugs are worth reimbursing (and which are not) on a population level, payers want 'value for money' and regulatory authorities are willing to consider real world data as complimentary to market approval submissions (to estimate drug value in the long run) (2, 27).

But there are some setbacks. For example, the Patient-Centered Outcomes Research Institute (PCORI) was commissioned as part of the US Affordable Care Act (ACA) to fund and conduct comparative effectiveness research, including large pragmatic trials, that would provide a better evidence-base for current health care practices (20). Though PCORI was evidently a response to the vast health care expenditures in the US, the initiative is ironically prohibited by the ACA from taking cost-effectiveness into account. Both in Europe and the US, pharmaceutical companies or other types of private sponsors have not demonstrated much interest in pragmatic trials for obvious reasons (28, 29). Gaining regulatory market approval is the main goal and explanatory trials are the way to achieve that goal. Real world evidence on comparative effectiveness, generated by pragmatic trials, is not required by regulatory authorities (such as the EMA or the US Food and Drug Administration, *FDA*) and most HTA agencies do not have the authority to require evidence from so-called 'head-to-head', direct comparisons. Pharmaceutical companies seem to have very little to gain from conducting pragmatic trials and a lot to lose: there is considerable

business risk in failing to prove comparative effectiveness at the expense of high trial costs (28). In the US—where reimbursement systems are prohibited to take cost effectiveness into account—the incentive for sponsors to demonstrate comparative effectiveness lacks almost completely (29). Ezekiel Emanuel, bioethicist and key advisor to Obamacare, writes candidly in his recent book 'Reinventing American Health Care' (2014) that "the general reaction to PCORI may be best characterized as one of frustration. It is perceived to have had a very slow start and has been quite timid in the research projects it has funded. The big clinical questions in need of comparative effectiveness research—ones fraught with controversy, variations in care patterns, and high costs—are not the ones PCORI is tackling" (30).

In Europe, however, there might be more opportunity for leverage. Germany, for example, serves one of the leading markets in Europe and rejects almost all indirect evidence for comparative effectiveness and explicitly demands direct evidence for national coverage (31). This evidence typically comes from pragmatic trials that use appropriate comparators. This means that, at least in Europe, one reason for private sponsors to engage in pragmatic trials is a growing interest in providing pharmacoeconomic evidence to obtain insurance coverage. In many European countries restricted reimbursement is given pending the outcome of post-marketing research (32, 33). Full, long-term reimbursement can be accelerated if real world evidence on the comparative effectiveness of new drugs becomes available at an earlier stage. Conversely, if a new drug fails to show added benefit to existing or cheaper treatment options, there is a compelling argument to withhold reimbursement. Ben Goldacre and Carl Heneghan similarly use companies' interest in securing greater market shares to incentivize what they call "better evidence" by suggesting to offer companies patent extensions or earlier market exclusivity in return for doing pragmatic trials (34). So at least in Europe, pragmatic trials evaluating new pharmaceutical interventions are increasingly being recognized as a serious option for addressing the current efficacy-effectiveness gap in drug research.

AMBIGUITIES IN THE DEBATE

The reason why it is important to note the difference between how the US and Europe employ pragmatic trials, is that it reveals that the timing and type of interventions compared are based on the type of decision-making they aim to inform: real world evidence can either be used to inform clinical practice retrospectively (different approved standard of care treatments are compared) or prospectively (a new treatment is compared with an approved standard). For some, the implementation of pragmatic trials in drug development is contradictory to the term (since in the pre-market setting the test intervention is not a usual care treatment). In addition, talking in terms of comparative effectiveness evaluations in drug development (typically understood as the period of drug discovery, research and development up until market authorization of the drug) is rather confusing as comparative effectiveness research (CER) constitutes, according to many, by definition post-market surveillance (phase IV) research. Awareness of the way commentators conceive of pragmatic trials when writing about their ethical challenges and potential solutions is crucial for a proper understanding of the debate.

Another challenge in discussing the concept of pragmatic trials is defining what a pragmatic trial exactly looks like (35). Over the past few years, the absolute number of newly PubMed-indexed titles per year containing synonyms of the term pragmatic trial has significantly increased. It was noted that some published trials with the term 'pragmatic trial' in the manuscript title were just as pragmatic as the average RCT (19). A likely explanation for this phenomenon is that all RCTs can be placed somewhere along a pragmatic-explanatory continuum as no trial is completely pragmatic nor completely explanatory. Thorpe and colleagues acknowledged this and developed the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) (recently refined to the PRECIS-2 tool) aimed at trialists to envisage what their trial design should look like in order for it to match the research question (12). Their work shows that research questions may display varying degrees of pragmatism and that as a consequence trial designs can (and should) be different—depending on the type of question—across nine domains. These domains consist of eligibility criteria, modes of recruiting participants, setting, organization, flexibility allowed to deliver the intervention, adherence measures, follow-up, outcome selection and primary analysis (3). Understanding RCTs in terms of being either more or less pragmatic/explanatory (rather than explanatory and pragmatic as dichotomous concepts) brings along some difficulties with discussing pragmatic trials in general terms. For example, at what point along the continuum can we no longer speak of a 'pragmatic' trial? Thorpe and colleagues do not answer this question, and for obvious reasons; as they do not visualize some sort of dichotomy, they probably would have answered that one should better adopt terms such as 'more pragmatic' and 'less pragmatic'.

THIS THESIS: AN ETHICAL ANALYSIS OF THE CONCEPT OF PRAGMATIC TRIALS

Increasing pragmatism in RCTs inherently calls for departures from the well-controlled features and conditions that are so paradigmatic of the traditional clinical trials enterprise. Similar to Carol Levine's statements about access to effective drugs and health knowledge in general, commentators have argued that the current level of ethical and regulatory scrutiny for pragmatic trials unnecessarily impedes research that is so critical to improving day-to-day patient care (36-39). More fundamentally, some question whether the traditional research ethics paradigm is still apt to effectively direct efforts towards protecting those who are most in need of protection (40, 41). Given the interest in—at least in Europe— pragmatic trials to enhance the evidence base for health care decision-making at the time of market approval, and given the inherent ethical tension that pragmatism seems to cause, the challenges and opportunities of pragmatic trials with new interventions merit ethical evaluation. The central question of this thesis is: Are pragmatic randomized trials with new interventions ethically feasible, and if yes, what challenges will need to be overcome, and how? I will use the terms 'early pragmatic trials' and 'pragmatic trials with new interventions' interchangeably in this thesis to refer to randomized trials conducted either before market authorization (late phase III) or shortly after market authorization (early phase IV) of the test interventions. The terms 'authorization',

'marketing', 'approval', 'registration', 'licensing' and 'launch' all refer to market access granted by a regulatory authority (mostly used in combination with either *pre-* or *post-*).

The central question of this thesis is addressed through a number of sub-questions, which are:

I. What are the ethical issues linked to real world studies in general, and pragmatic trials in particular, by stakeholders in the field and in the academic literature?

II. What are the empirical and ethical assumptions underlying these issues and challenges?

III. To what extent are these issues likely to occur (testing empirical assumptions) and what are the normative implications of proposed solutions (testing normative consequences)?

IV. How do these findings affect our thinking about the ethical constraints and opportunities for pragmatic trials in earlier stages?

V. How can the tension between pragmatism and traditional research ethics guidance potentially be reconciled for pragmatic trials in earlier stages?

In order to answer question (I), I start out with an exploration of the ethical issues in the broad sense of pragmatic trials, along with those issues emerging in the context of practice-based comparative effectiveness research and real world evidence generation more generally. **Chapter 2** uses the methodology of a systematic literature review to roughly map the types of ethical issues that have been related to studies or RCTs that could be considered 'pragmatic'. I searched the available literature for papers referring to the ethics of basically any type of comparative effectiveness study or self-defined pragmatic, practical, real world or large simple trial. This study also makes a first step towards addressing question (II) by attempting to characterize the identified issues in terms of their underlying empirical and normative assumptions. **Chapter 3** similarly addresses questions (I) and (II) but uses a qualitative approach to obtain answers that reflect actual experiences and perceptions of stakeholders in the field of drug research. From these two studies, similar results were obtained reflecting challenges regarding risk determination, ethical oversight, ensuring the value of pragmatic research and—most notably—the issue of informed consent.

Chapter 4 builds in part on the answers to question (I) to pinpoint specific issues concerning the eligibility, recruitment and retention of participants in pragmatic trials by presenting a narrative, literature-based overview. Most significant in ethical terms, is that this chapter again stresses the challenges posed by informed consent to the practicability of pragmatic trials and adds to the array of challenges the inclusion of vulnerable subjects.

Chapter 5 sets out from the combined findings in the previous chapters and addresses question (III) with respect to the issue of informed consent. Here, I critically assess the challenges informed consent is believed to pose to pragmatic trials by testing some of the underlying empirical assumptions regarding practicability. Subsequently, I discuss four proposed alternative informed consent procedures and their normative consequences.

In **Chapter 6** the transition is made towards making more normative assertions about what changes morally when pragmatism is employed in earlier stages of clinical research (question IV). Here, I analyze to what extent modifications to regulatory consent procedures would be ethical for pragmatic trials with new interventions (either in the pre-market or early post-market setting), by first identifying broadly accepted necessary conditions for modifications of informed consent (waivers and alterations) and then applying those criteria to the pre-market and early post-market context.

Chapter 7 attempts to make a first move in the direction of reconciling potential conflicts between pragmatism and ethics regulations (question V). This piece deals with the question why deviations from the traditional research ethics paradigm would be defensible for a pragmatic trial. In this chapter, I remark that apart from the generally accepted conditions for such deviations—namely, that the trial poses no more than minimal risks and that execution would be impracticable otherwise—commentators seem to justify pragmatic designs through their anticipated societal benefits, or *social value*. My argument is that such a social value requirement is laudable from a moral point of view, yet requires specification for it to be properly operationalized in the ethical assessment of pragmatic trial designs. Consequently, three determinants from common claims about a pragmatic trial's social value are constructed: the extent to which the research question has real world relevance, the trial design's ability to generate a real world answer and the probability of direct uptake of the results by decision-makers in practice.

Ultimately, **Chapter 8** presents a general discussion of the most noteworthy findings of the previous studies and, more importantly, explicitly addresses question (V) about the ways in which pragmatic goals might be advanced while appeasing potential ethical concerns. Subsequently, I propose three accessible and ethically responsible ways to move forward in promoting pragmatism in randomized trials at market access.

CHAPTER 2

PRAGMATIC RANDOMIZED TRIALS IN DRUG DEVELOPMENT POSE NEW ETHICAL QUESTIONS: A SYSTEMATIC REVIEW

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ABSTRACT

Implementation of pragmatic design elements in drug development could bridge the evidence gap that currently exists between the knowledge we have regarding the efficacy of a drug versus its true, comparative effectiveness in real life. We performed a review of the literature to identify the ethical challenges thus far related to pragmatic trials. The three central ethical questions identified for pragmatic trials are: (I) what level of oversight should pragmatic trials require; (II) do randomized patients face additional risks; and (III) is a waiver of informed consent ethically defensible? Despite the fact all reviewed publications dealt with post-launch pragmatic trials, these results could serve as an important starting point for conceptualizing what challenges could potentially arise in the pre-launch setting.

INTRODUCTION

During recent years, demand has increased for high-quality scientific evidence that compares the relative effectiveness of new drugs against existing standards in routine clinical practice. Such comparative effectiveness research (CER)—aimed at comparing the effectiveness and safety of alternative preventive, diagnostic and treatment options (42)—is considered essential for health care decisions, evidence based guidelines and reimbursement (36). In drug research and development, CER is typically performed after market authorization. What is known about new drugs at registration is derived from phase III randomized clinical trials assessing efficacy under 'optimized' or 'equalized' conditions, rather than real life conditions. The post-registration use of drugs typically concerns different use as well as different users, limiting the abilities of health care providers to extrapolate pre-launch findings to a broader and less homogeneous patient population (38). This current evidence gap has resulted in large, complex post-launch trials assessing the comparative effectiveness of newly marketed drugs. Not only have such trials shown to drive up costs exponentially (38), they also have been said to often lack the design to generate the real-world evidence needed to adequately improve health care decision-making (43).

Pragmatic randomized clinical trials, designed to answer clinically relevant research questions under real world conditions (13), have the ability to bridge this evidence gap within CER (36, 44, 45). More extensive use of pragmatic trial designs has been advocated, as well as earlier implementation in the drug development process. The IMI GetReal consortium is a multi-stakeholder public-private partnership that aims to explore new design strategies to provide a variety of stakeholders with an enhanced evidence base for health care decision-making with regard to the comparative effectiveness of new drugs (8). However, the adoption of real world objectives in the pre-launch drug development program creates many operational, methodological, regulatory and ethical issues. We imagine that new usages of pragmatic trials pose new ethical questions as these trials are sought to be woven into routine clinical practice, studying more heterogeneous study populations under less controlled conditions. As a consequence of the increased integration of drug research and clinical care the roles and responsibilities of patients, physicians, researchers and regulators could change. In this evolving landscape, the existing ethical framework for effectiveness research might no longer be adequate.

To identify the ethical challenges that have been related to pragmatic randomized clinical trials thus far, we performed a systematic review of the available literature. We did not confine our literature search to either pre-launch or post-launch research in order to cover all relevant issues presented in the literature. In our synthesis of the relevant publications, however, we will distinguish between the ethical issues specifically related to *pre-launch* studies and those specifically related to *post-launch* studies, because we acknowledge that the arguments presented might not always apply to both.

STUDY METHODS

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (46).

Search and eligibility criteria

The PubMed, EMBASE and Scopus databases were searched by title and abstract using synonyms of the terms 'pragmatic trial' or 'comparative effectiveness' and 'ethics' for records published from 1990 through August 2014 (Table 2.1). Publications were included for further evaluation when either the Title or Abstract referred to a discussion likely to mention ethical issues of pragmatic clinical trials or any other kind of interventional practice-based CER activity.

Table 2.1. Syntax of search terms (search performed on August 26, 2014).

Database	Search[a]	Hits
PubMed (MEDLINE®)	((((ethic*[Title/Abstract]) OR moral*[Title/Abstract]) OR informed consent[Title/Abstract])) AND ((((((((((((pragmatic trial*[Title/Abstract]) OR pragmatic randomized[Title/Abstract]) OR pragmatic randomised[Title/Abstract]) OR pragmatic clinical[Title/Abstract]) OR pragmatic stud*[Title/Abstract]) OR randomized pragmatic[Title/Abstract]) OR randomised pragmatic[Title/Abstract]) OR practical randomized[Title/Abstract]) OR practical randomised[Title/Abstract]) OR practical trial*[Title/Abstract]) OR practical clinical trial*[Title/Abstract])) OR relative effectiveness[Title/Abstract]) OR comparative effectiveness[Title/Abstract])	98
EMBASE	See PubMed	139
The Cochrane Library	See PubMed	389

[a]Search terms were used in title and abstract fields only.

Selection

At full text screening, all publications were excluded that did not provide a sufficient degree of ethical argumentation. Reference lists of the selected studies were additionally screened in search of related articles missed in the initial search. Such a 'snowballing' technique was preferred to the inclusion of additional terms into the search string as this would lead to an unmanageable number of hits. Arguments presented in the relevant publications were grouped according to the development stage they pertained to (either pre-launch or post-launch) and were qualitatively reviewed.

STUDY RESULTS AND DISCUSSION

Literature search

The literature database search resulted in a total of 439 unique publications (Figure 2.1). Full texts of 14 publications were included for final review. Ten additional relevant titles were uncovered by screening the reference lists of the publications included after the initial search. Of these ten additional records, six were published without an abstract in *The Hastings Center Report*, explaining why these publications were initially missed by our Title/Abstract search. Thus, 24 publications were deemed relevant for final review (Table 2.2). All synthesized publications consisted of review articles or commentaries and pertained to post-launch real-world evidence. No publications on pragmatic trials in the pre-launch setting were encountered.

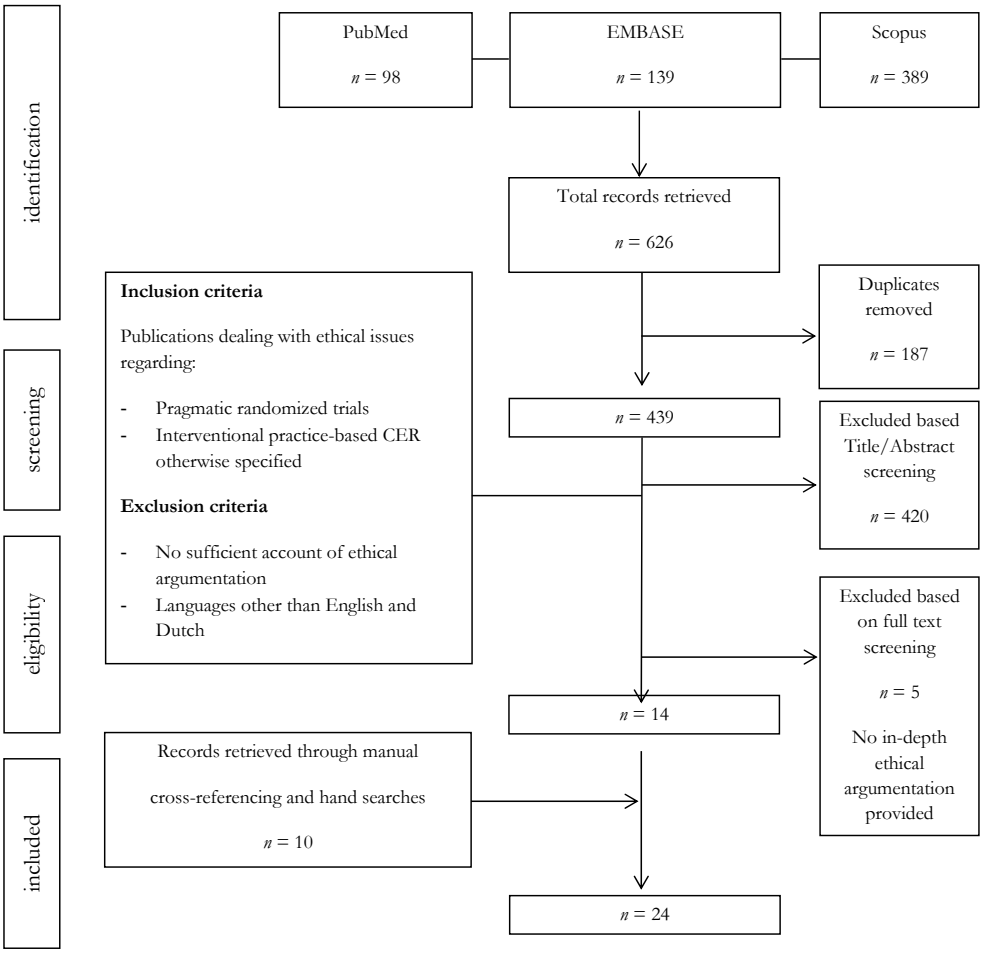

Figure 2.1. Flow diagram of the selection and inclusion of publications. Abbreviations: CER, comparative effectiveness research.

Table 2.2. Study characteristics of reviewed publications.

No.	Authors	Year	Country of origin	Terminology used for type of research	Ethical oversight	Risks of randomization	Informed consent
1	Faden *et al.* (41)	2013	US	Practice-based research (CER and quality improvement)	x		
2	Selby and Krumholz (48)	2013	US	Practice-based research (CER and quality improvement)	x		
3	Van Staa *et al.* (49)	2014	UK	Pragmatic randomized trials (CER) in primary care	x		
4	Kass *et al.* (40)	2013	US	Practice-based research (CER and quality improvement)	x		
5	Platt *et al.* (37)	2014	US	(Randomized) CER	x		
6	Menikoff (50)	2013	US	Interventional randomized trials	x		
7	Kupersmith (51)	2014	US	CER, practice-based research	x		
8	Grady and Wendler (52)	2013	US	CER, practice-based research	x		
9	Largent *et al.* (53)	2013	US	CER, practice-based research	x		
10	Eapen *et al.* (38)	2014	US	Large simple trials		x	
11	Sugarman and Califf (43)	2014	US	Pragmatic randomized trials		x	
12	Van Staa *et al.* (44)	2012	UK	Pragmatic randomized trials in primary care		x	
13	Chalkidou *et al.* (45)	2012	UK	Pragmatic randomized trials in CER		x	
14	Kass *et al.* (54)	2012	US	CER, practice-based research		x	
15	Truog *et al.* (55)	1999	US	RCTs		x	x
16	Faden *et al.* (24)	2013	US	CER, practice-based research			x
17	Faden *et al.* (47)	2013	US	CER, practice-based research			x
18	Kim and Miller (56)	2014	US	Pragmatic randomized trials			x
19	Elsayyad (57)	2014	US	Pragmatic randomized trials			x
20	Modi (58)	2014	US	Pragmatic randomized trials			x
21	Curro *et al.* (59)	2013	US	Practice-based randomized trials			x
22	Feudtner *et al. (60)*	2013	US	Randomized trials in CER			x
23	Wendler (61)	2013	US	RCTs involving standard of care interventions			x
24	Spellecy *et al.* (62)	2013	US	RCTs (CER) involving standard of care interventions			x

Abbreviations: CER, comparative effectiveness research; RCTs, randomized controlled trials.

What level of oversight do post-launch pragmatic trials require?

There is contention about the question to what extent the traditionally maintained research-treatment distinction is still of moral relevance for determining the level of required oversight in post-launch CER. Comparative effectiveness trials have been described by Faden and colleagues as an illustrative example of a learning activity that generates and applies scientific evidence through the integration of research and routine clinical care (47). Therefore, pragmatic trials have been called upon in support of a so-called 'learning health care system' that promotes ongoing learning activities that have the ability to improve current decision-making in health care (41). Results from such CER activities rely heavily on the (near) full participation of the targeted study population (48) as well as their intended simple nature (49). In a learning health care system, Kass and colleagues argue that maintaining the traditional distinction between clinical research and care to determine the level of ethical governance threatens adequate conduct of practice-based CER. The authors advocate a rejection of the research-treatment distinction as it additionally fails "to identify which activities warrant ethical review and to determine when patients are at risk and in need of oversight protection" (40). Kass and colleagues argue that labeling certain activities as 'research' currently indicates that these activities are subject to more stringent regulation, despite the fact that they might involve similar or even less risk than routine practice—a view coined 'research exceptionalism' by Wilson and Hunter (63).

The classic definition of clinical research as "a systematic investigation designed to produce generalizable knowledge" is said by Kass and colleagues to be of decreasing value because nowadays health care delivery is bound to the same requirements of systematic data collection and quality improvement (40). Some also contest assumptions that clinical research involves greater burdens and risks than clinical care, and that treatment assignment decisions are made less arbitrarily in clinical care (37, 40, 41). Accordingly, Faden and colleagues constructed an ethics framework to facilitate the transformation of the current system towards a learning health care system (41). The first feature of the framework is the rejection of the moral relevance of the research-treatment distinction in a learning health care system. Second, the framework maintains the presumption that institutions, health care workers and patients have a moral obligation to contribute to practice-based research activities, from which all parties benefit.

Although many have praised the call for a more extensive integration of post-launch CER and clinical care, objections have been raised against the ethical framework, at least against some of the obligations that it entails. Some commentators have raised concerns about the suggestion that a limited number of practice-based research activities could potentially proceed without express informed consent, questioning the statement put forward by Faden and colleagues that these activities truly "have little, if any, effect on patients' interests or rights" (41). Menikoff questions whether there really is no real good reason for a person to prefer one treatment arm over the other in trials that involve approved and widely used drugs (50). Kupersmith states that the moral obligations of patients and physicians to participate in practice-based research are not ethically equivalent for patients because they bear risks while they are in a dependent relationship with their treating physician (51). In addition, Kupersmith argues that the affirmative obligation for patients to be partners in learning health care systems

cannot exist ethically without a reciprocal duty for researchers to generate valid information through these learning activities, and to translate the findings into clinical practice. For nurses and physicians, Grady and Wendler point out that the moral obligation also suggests that when they focus primarily on what is best for their patients they are acting unethically, unless they direct these activities towards learning what is best for future patients as well (52).

Furthermore, it is debated whether the evidence that suggests subjects participating in a pragmatic randomized trial fare no worse than patients receiving the same treatments in practice is convincing enough. Largent and colleagues remark that it is important to distinguish the empirical from the normative dimensions of the research-treatment distinction: that care as usual may be suboptimal or entail unnecessary risks does not mean its use is automatically justified in clinical research (53).

Although all of the above-mentioned commentators equally express concern that overregulation (i.e., regulation that is not essential to human subjects protection) hampers endeavors to improve health care decision-making, debate revolves around the question regarding to what extent rejection of the currently maintained research-treatment distinction ensures adequate protection of patient subjects enrolled in learning activities, such as pragmatic randomized trials, involving approved products. From the literature it appears that to reject the research-treatment distinction is consequently to reject research exceptionalism. Instead of adhering to the concept of research exceptionalism (as many oversight bodies are said to currently do, displayed in for instance the Good Clinical Practice guidelines), it is argued that one ought to look at the risk-benefit ratio of the activities themselves, without adding extra weight in the balance just because it concerns clinical research (40, 41). A prominent example named in the literature is the act of randomization, which will be discussed in the next section. From the debate in the literature about the moral relevance of the research-treatment distinction in a learning health care system, it follows that the level of ethical review and oversight a post-launch pragmatic trial is perceived to require depends on the extent to which one accepts or rejects research exceptionalism as an essential means for ensuring human subject protection in post-launch CER.

What additional risks do randomized patients face in a post-launch study?

Randomization of a large population of representative patients has been described as an essential element of practice-based CER. A pragmatic trial aims to interfere as little as possible with usual care conditions, while maintaining randomization of study treatments to allow possible cause-effect evidence (38, 43-45, 49). Nevertheless, randomization in clinical practice has proven to be a thorny issue. This first and foremost relates to the idea that research and clinical care are two cross-cutting practices, as we have identified in the previous section. When randomization is introduced into clinical care to study approved treatment strategies, the activities are labeled as interventional research requiring ethical oversight (44, 49). The underlying rationale seems to be the notion that individual patients are likely to have better outcomes when treatment decisions are based on the clinical judgment of physicians rather than when treatment allocation is performed at random (64, 65).

The perception that random allocation in itself is an activity that may potentially lead to greater than minimal risk for the patients involved, has resulted in full ethics committee review for randomized trials in the United States (66). Kass and colleagues state that the question whether this notion is correct still remains unresolved for trials investigating commercially available and widely used drugs (54). Truog and colleagues argue that when physicians do not know which of two approved treatments for the same condition is superior they can arbitrarily assign these treatments to their patients in the context of clinical care without external scrutiny, while in the context of a clinical trial such activities encounter substantial hurdles (55).

Kass and colleagues (40) cite evidence (67-69) that suggests that, when there is a state of 'clinical equipoise' (i.e., genuine uncertainty in the expert community about the net superior treatment), randomization in fact does not necessarily lead to worse clinical outcome for patients compared to assignment choices based on clinical judgment by physicians. One of the cited publications, a systematic review performed by Gross and colleagues demonstrated that in the majority of reviewed studies there were no significant differences in clinical outcomes between randomized and non-randomized patients (whose treatment allocation was based on clinical judgment and/or patient preferences) who were classified as having similar health status at baseline (67). The authors note that many of the included studies assessed a single primary endpoint (i.e. mortality), and that there might have been differences in the probability of other adverse events or quality of life between trial participants and non-participants, as well as differences in the perceived burden due to additional research procedures. Because the review by Gross and colleagues only included studies that also provided non-participants access to the investigational product, the authors state that it is unclear whether the results can be extrapolated to pragmatic randomized trials that include newer therapies that are not available outside the research setting, as would be the case in pre-launch trials.

Sugarman and Califf state that making decisions about what research activities consist of more than minimal risk can prove complex, despite the seemingly straightforward definition provided by US federal regulations (43). The authors express concerns about the preclusion of randomization for CER merely to avoid the more 'burdensome' type of ethical oversight compared to the type required for quality improvement. It is feared that non-randomized real world studies may be conducted in a way that does not enable reliable conclusions for clinical practice (e.g., due to design shortcomings). The challenge in the design and conduct of pragmatic randomized trials therefore lies in identifying the risks and uncertainties, and determining how one ought to assess these risks and uncertainties in relation to the care patients receive outside the trial in order to justify randomization.

Is a waiver of informed consent in post-launch randomized trials ethically defensible?

The requirement to obtain informed consent from research participants is one of the most important ethical principles in biomedical research (70, 71). Likewise, physicians need to seek informed consent from their patients before the start of every procedure for them to be able to act out their autonomy. Truog and colleagues argue that the requirements for informed

consent in clinical research are—without sufficient reasons—different from those required for the same treatments in routine care (55). In routine care, Truog and colleagues suggest that whether a physician needs to obtain general or specific consent depends on the risks related to the procedure, whereas in clinical research the consent is always required to be specific. They believe that "as with clinical care, in the case of many randomized, controlled trials, the patient's participation can and should be considered to be authorized by his or her general consent for treatment and that specific consent should not be required" (55). According to Truog and colleagues, the conditions for a waiver of informed consent for randomized controlled trials are that: (I) all treatments offered in the trial can be offered outside the trial without specific informed consent; (II) treatments do not involve more than minimal additional risk in comparison with any of the alternatives; (III) genuine clinical equipoise exists among the treatments; and (IV) no reasonable person should have a preference for one treatment over another.

Faden and colleagues consider a waiver of informed consent for randomized comparative effectiveness trials acceptable under similar conditions, adding that patients for whom the treatment is considered inappropriate should be excluded, and that liberal changes and stoppage rules can be applied by physicians when they believe it to be in the best interest of their patients (24, 47). An example of such a study, as presented by Faden and colleagues, consists of a pragmatic trial evaluating two approved antihypertensive treatments, both well tolerated and with low adverse events rates, in which the only deviation from clinical practice is that treatment allocation is performed randomly rather than by physician preference (24). Key features of this design are that only patients for whom there is no evidence favoring one treatment over the other would be enrolled and that physicians have the authority to override enrollment and randomization at all times. The authors believe that with this type of design a pragmatic randomized study may proceed ethically without requiring express informed consent from participants, under the condition that "the study will be implemented in a health care context where patients are regularly informed that learning activities involving randomization are occasionally permitted without express consent, after careful review to ensure patients' interests and rights are protected" (24). However, when patients enrolled in a near-identical study would have to undergo extra, non-care related procedures that serve the learning activity only (e.g., additional clinic visits for blood pressure checks), Faden and colleagues declare that it would be disrespectful not to inform patients that the additional visits are for the exclusive purpose of the study and can be declined. Consequently, concealing randomization is considered deceptive.

Faden and colleagues propose that in a learning health care system an ethics oversight panel determines whether certain CER activities "fall above or below a threshold of negative effect" on expected clinically relevant outcomes (47). Activities involving only negative effects below the threshold can be integrated into routine practice without specific notification or obligation to seek informed consent from patients (though they will be publicly notified in their community about the system). Patients who are eligible for CER activities that are determined by the panel to have 'minor but still meaningful effects on patients' interests' should be notified about the option to decline participation. Studies considered to involve negative effects above the threshold will require prospective, written informed consent, according to the authors.

Van Staa and colleagues have expressed concerns towards the "time consuming and expensive" requirements for informed consent and regulatory oversight in post-launch pragmatic randomized trials comparing two treatments that "have already been shown to be safe and are in widespread and routine use" (44). The authors state that guidelines for informed consent are a substantial barrier to research into routine treatments, whereas these guidelines are not based on empirical evidence and are even contradictory at times.

Kim and Miller warn against full waivers of informed consent for randomized trials involving standard of care interventions, calling the assumption that a patient cannot have any meaningful base for a treatment preference unjustifiably paternalistic (56). The authors state that some people do have a meaningful base for wanting to be informed that they are enrolled in a clinical trial, where others could have a meaningful preference based on experience from their relatives or friends. In the previous section on randomization, we have identified that there can exist additional (unreported) parameters, apart from the primary outcome, that provide a base for patient preferences, such as dosing scheme or particular discomforts related to the drug (67). Kim and Miller subsequently argue that it is incorrect to assume that autonomy is not infringed as long as health care interests are protected while the benefit gained from concealing randomization is minimal (56). This view is shared by different commentators, adding that informing patients about treatment options is a matter of respecting a person's dignity (57) and that the clinician-researcher must be particularly aware of the potential conflict of interest (58). A patient must be able to trust their physician explicitly, knowing they will receive a standard of care that is not compromised by research agendas (59).

Feudtner and colleagues argue that, in order to provide ethically appropriate informed consent in a pragmatic trial, investigators should consider, manage, and communicate with potential participants about a set of nine different types of risks that might be encountered during trial participation (60). Foremost, the authors state that patients should be informed that the relative difference between the two treatment arms is currently unknown; as a result patients could be potentially assigned to an inferior arm involving harm. The authors acknowledge that clarification could cause psychological discomfort in patients who find uncertainty distressing. However, instead of attempting to avert such distress by means of concealment, Feudtner and colleagues stress that investigators should inform potential patient participants that these risks also exist for patients receiving the standard of care intervention outside the trial and that their outcomes will probably be the same if they do not participate. Wendler further elaborates on the risks that need to be disclosed in a pragmatic trial, arguing that the informed consent form should only list those risks that are unique to the research (61). Spellecy and colleagues add to this that the goals of the study should also be clarified during the informed consent process in order to comply with the principle of respect for persons (62).

CONCLUDING REMARKS: IMPLICATIONS FOR PRE-LAUNCH PRAGMATIC TRIALS

To the best of our knowledge, this review is the first to explore the ethical challenges of pragmatic comparative effectiveness trials using a literature-based approach. Because thinking about pragmatic trials in ethical terms is still somewhat it its infancy, and in addition is substantially complex, we believe our findings serve as an important starting point for different stakeholders in the field of drug development and CER to conceptualize what challenges could potentially arise when pragmatic design elements are introduced at an earlier stage, perhaps even before market access.

The three central ethical considerations we identified in the post-launch environment consist of the questions: (I) what level of oversight do pragmatic trials require; (II) what additional risks do randomized patients face; and (III) is a waiver of informed consent in post-launch randomized trials ethically defensible? Our overview of the ethical challenges is limited in the sense that there is no literature thus far describing the issues specifically related to pre-launch pragmatic trials. All reviewed publications dealt with the ethical issues of pragmatic trials after regulatory approval of the compared products. The ethical questions raised in the literature therefore cannot simply be extrapolated to the pre-market registration setting. Before approval of a pharmaceutical product there is more uncertainty about the efficacy of the drug and its safety profile. Thus, many of the arguments put forward in the reviewed publications will most probably not withstand scrutiny when the treatments provided in the trials are not available outside the trial.

Nevertheless, we believe that the three ethical questions, or considerations, that were derived from our analysis of the literature on post-launch trials are valuable to conceptualizing what challenges could potentially arise in the pre-launch setting. Although discussions about waivers of informed consent will most probably not have a place in the pre-launch setting, shaping our thoughts about what adequate oversight systems constitute does seem an equally relevant issue for pragmatic trials involving unregistered products versus standards of care. This also applies to justifying randomization of real world patients and the specifications of the informed consent procedure. One of the shortcomings of this study was that particular ethical challenges described in publications of actual pragmatic trials might have been missed (perhaps because they would be only briefly mentioned throughout the paper). Also, ethical publications that elaborate on what we consider pragmatic trials, but which use other terms to describe the type of research might not have been covered by our search. We emphasize that the nature of the content of the reviewed publications does not allow for proper quality assessment; however we do not consider this detrimental to the study because our aim was to present the first explorative overview of the ethical issues that have been raised thus far. Our study rather serves to kick-start future ethical deliberation on this subject of increasing relevance. To further complete this overview, conceptual work on the matter as well as qualitative research which canvasses the experiences and views of different stakeholders in the field of drug research and CER is warranted.

CHAPTER 3

STAKEHOLDERS' VIEWS ON THE ETHICAL CHALLENGES OF PRAGMATIC TRIALS INVESTIGATING PHARMACEUTICAL DRUGS

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ABSTRACT

Background

We explored the views of key stakeholders to identify the ethical challenges of pragmatic trials investigating pharmaceutical drugs. A secondary aim was to capture stakeholders' attitudes towards the implementation of pragmatic trials in the drug development process.

Methods

We conducted semi-structured, in-depth interviews among individuals from different key stakeholder groups (academia and independent research institutions, the pharmaceutical industry, regulators, health technology assessment (HTA) agencies and patients' organizations) through telephone or face-to-face sessions. Interviews were structured around the question what challenges were experienced or perceived during the design, conduct and/or review of pragmatic trials. Respondents were additionally asked about their views on implementation of pragmatic trials in the drug development process. Thematic analysis was used to identify the ethically relevant features across data sets.

Results

We interviewed 34 stakeholders in 25 individual sessions and 4 group sessions. The four perceived challenges of ethical relevance were: less controlled conditions creating safety concerns, comparison with usual care potentially compromising clinical equipoise, tailored or waivers of informed consent affecting patient autonomy and minimal interference with real world practice reducing the knowledge value of trial results.

Conclusions

We identified stakeholder concerns regarding risk assessment, use of suboptimal usual care as a comparator, tailoring of informed consent procedures and ensuring the social value of pragmatic trials. These concerns increased when respondents were asked about pragmatic trials conducted before market authorization.

INTRODUCTION

The majority of randomized controlled trials (RCTs) in drug research are explanatory trials that focus on drug safety and efficacy (17, 72). They are currently accepted as the highest source of evidence for market authorization decisions by regulatory bodies. However, explanatory approaches provide limited knowledge about how newly marketed drugs work once applied under 'real world' conditions and/or when compared with existing treatments for the same condition in clinical practice (73, 74).

The lack of generalizability in drug RCTs has led to a knowledge gap between what we know about the isolated biological effects of a pharmaceutical compound and what we know about its comparative effectiveness in daily medical practice (36-38, 44, 45). In 1967, Daniel Schwarz and Joseph Lellouch published their landmark paper in which they differentiate between explanatory and pragmatic RCTs (13). The authors noted that too often trialists were not properly addressing their research questions due to failure to match their trial design to the type of answers they were seeking. According to the authors, the explanatory approach should be used when the aim is to obtain information about whether a treatment works under ideal conditions. Hereto, a highly selected study population is required and extraneous effects (such as the placebo effect) ought to be ruled out. The pragmatic approach, on the other hand, has the aim of directly informing health care professionals by comparing treatments under the conditions they would be applied in practice (which includes extraneous effects) (1). In pragmatic research, existing treatments can be tested against one another for their comparative effectiveness in real life, or new treatments are compared with (a variety of) usual care for a specific condition. Because of the type of questions they seek to answer, pragmatic trials generate so-called 'real world evidence' which has potential to overcome the current knowledge gap between drug efficacy and effectiveness.

Though no trial is completely explanatory nor completely pragmatic, trial designs can be assessed as being either more explanatory (idealized circumstances) or more pragmatic (resembling usual or real world care) within a continuum (12). A trial that does not apply strict exclusion criteria (to better reflect the real world population), that recruits patients with no more effort than would be used to engage patients in usual care and that allows physicians considerable flexibility in how they deliver the intervention, can be called more pragmatic than explanatory.

Recent collaborative initiatives to facilitate the conduct of pragmatic trials consist of the National Institutes of Health (NIH) Health Care Systems Research Collaboratory (22) and the US Patient-Centered Clinical Research Network (PCORnet) (21). In general terms, their mission is to increase the quality and reduce the costs of clinical research through stakeholder engagement and use of large amounts of health data. Pragmatic trials thus far have almost always been discussed as post-market authorization research. This renders pragmatic trials for many almost synonymous to pragmatic comparative effectiveness trials. However, real world evidence on the comparative effectiveness of drugs can in principle also be collected by pragmatic trials in earlier phases of the drug life cycle. The multi-stakeholder IMI GetReal

consortium has the objective of exploring new methods to incorporate real world evidence earlier into the process of drug development to better inform health care decision-makers about the real world effectiveness of new drugs at market authorization (8).

Though regulatory bodies do not demand real world studies for all approved products per se, the EMA does support the goals of pragmatic trials through the development of so-called 'adaptive pathways'. Adaptive pathways, according to the EMA, is a scientific concept for drug development which allows for early and progressive patient access to new drugs through conditional licensing, which requires real world evidence collection to support clinical trial data through an iterative process (75). For conceptual clarity, we refer to pragmatic trials as RCTs that are "[d]esigned for the primary purpose of informing decision-makers regarding the comparative balance of benefits, burdens and risks of a biomedical or behavioral health intervention at the individual or population level" (a definition that does not distinguish between pre- and post-market authorization research) (10). We use real world comparative effectiveness as a measure that can be evaluated both before and after market authorization of the tested drug, though we acknowledge that comparative effectiveness research (CER) is typically conducted with standard of care treatments.

Considering recent initiatives to implement pragmatic trials in routine health care settings—especially in earlier phases of the drug life cycle—parallel ethical evaluation appears warranted (43). Such evaluation seems to become even more compelling as recent debate has particularly focused on the ethical acceptability of pragmatic trials in terms of altering informed consent requirements (76), the inclusion of vulnerable populations (77), determining adequate oversight practices (78), and the harms and benefits patients face in pragmatic trials (79). In the process of articulating the ethical challenges of pragmatic trials with pharmaceutical drugs—especially when implemented in drug development—stakeholders' views are an important source of information.

We performed a qualitative study to obtain insight into stakeholders' views on the ethical challenges of pragmatic trials comparing pharmaceutical treatments. To trace potential ethically relevant differences between pre-market and post-market authorization pragmatic trials, a secondary aim was to capture stakeholders' attitudes towards the implementation of pragmatic trials in drug development.

METHODS

Study design and setting

This descriptive qualitative study aims to identify the experiences, perceptions and attitudes from the point of view of key stakeholders to explore the ethical challenges of pragmatic clinical trials investigating pharmaceutical drugs. Interviewees were identified from global stakeholders involved in the conduct of pragmatic trials and real world studies, including stakeholders within academia, non-profit research institutions, contract research organizations (CROs), the pharmaceutical industry, regulatory authorities, health care insurers and health technology assessment (HTA) agencies as well as patient organizations. Table 3.1 provides a description

of stakeholder characteristics. Since experience with pragmatic trials in this field is relatively scarce, respondents were identified by means of purposeful sampling. In total 42 stakeholders were approached by email for interviews; of these, two stakeholders declined an interview due to time constraints and six of them were non-responders. Semi-structured, in-depth interviews were conducted face-to-face or, when distance was a problem (e.g., for respondents located outside Europe), by telephone or through an online connection. Group interviews were set up with respondents who were involved in the same projects within one company or institution.

Selection of participants

An invitation email with an information sheet was sent to target participants identified through the network of the IMI GetReal consortium, and by following recommendations from the interviewees (so-called snowball sampling) (80). Stakeholders were first asked to describe their experience with either designing, conducting or assessing real-world studies in general or, more specifically, with pragmatic clinical trials. Subsequently, they were asked to elaborate on any relevant challenges or hurdles that were faced during the process. These challenges could either pertain to specific pragmatic design aspects as well as to more general complexities throughout the whole process of designing, conducting or assessing a pragmatic trial. When a respondent put forward a study he or she was involved in which was relevant in terms of ethical challenges, this study was pinpointed for further enquiry if needed. Respondents were, in addition, asked to specifically reflect on implementation of pragmatic trials before regulatory approval of the test intervention. The design of the Salford Lung Study was described to stakeholders as an example of a pre-market authorization pragmatic trial (see Box 3.1) (25). Recruitment was terminated when saturation was reached, indicating that no new thematic content was found (81).

All interviews were conducted between April and October 2014. They were conducted by a trained interviewer (SK) and took approximately 45-60 minutes. All interviews were audio recorded with permission of the interviewees and transcribed verbatim. According to the Dutch Medical Research Involving Human Subjects Act, this type of study is exempt from ethical review. Verbal consent was obtained from all respondents prior to the interviews. The anonymity of respondents and institutions was maintained in the interview transcripts.

Analysis and reporting

Transcripts of the interviews were coded in NVivo qualitative data analysis software (version 10, QSR International Pty Ltd.). Thematic analysis was used to identify ethical considerations across data sets (82). All interview transcripts were coded by SK. For validation purposes, 14 out of 29 interviews were double-coded by two additional reviewers (GvT and AM), after which any discrepancies were discussed until consensus was reached. We used the consolidated criteria for reporting qualitative research (COREQ) checklist to guide the conduct, analysis and reporting of this study (83).

Table 3.1. Backgrounds of interviewed stakeholders.

Characteristics respondents	Nr. 34
Sex	
Male	21
Female	13
IMI GetReal member	
Yes	6
No	28
Country of professional residence	
The Netherlands	9
United Kingdom	8
Germany	5
France	2
Belgium	1
Denmark	1
United States	7
Israel	1
Experience with pragmatic trials	
Yes	23
No	11
Stakeholder group	
Pharmaceutical industry	16
Academia/non-profit research institutions	6
Contract research organizations (CROs)	4
Health technology assessment (HTA)	2
Regulatory bodies	2
Patient representatives	2
Clinicians	1
Health insurers	1

RESULTS

Thirty-four stakeholders were interviewed in 25 individual interviews and four group interviews with a response rate of 34/42 (81%). After analysis of the interview data, we identified four ethically relevant themes from the respondents' views on the ethical challenges of pragmatic trials investigating pharmaceutical drugs.

Less controlled conditions create safety concerns

Respondents believed that pragmatic trials do not have the degree of control as is required for more traditional RCTs, predominantly due to lack of a highly directive study protocol that physicians are instructed to follow. Physicians were thought to have considerable flexibility in how they prescribe the test drug in a pragmatic trial, i.e., prescribing the test drug as they would do with any newly marketed drug. It was also feared that physicians might prescribe

Box. 3.1. Features of the Salford Lung Study (GSK).

- Open-label pre-license phase III pragmatic randomized effectiveness trial (2012-2016)
- Population: patients with asthma treated in general practice in Salford (United Kingdom)
- Test arm: Once-daily long-acting β2-agonist (LABA)/inhaled corticosteroid (ICS) (fluticasone furoate + vilanterol) in novel dry powder inhaler
- Comparator arm: continuation of usual asthma treatment (ICS or ICS/LABA)
- Primary outcome: improvement in asthma control (Asthma Control Test)
- Follow-up time: 12 months by means of electronic health records
- Efficacy and safety data available for more than 6400 patients from completed RCTs at **the** time of study initiation

doses beyond a drug's label indication creating safety issues for the patients enrolled. This raised critical questions with respect to the responsibilities that investigators have towards protecting the interests of the patients enrolled in a pragmatic trial, if indeed conducted under less-controlled conditions.

On pre-market authorization pragmatic trials, respondents perceived less-controlled conditions as particularly problematic, assuming that at these stages safety and efficacy data for and clinical experience with the test drug is limited. Stakeholders supposed that in a pragmatic trial minimal interference in real world conditions is strived for, indicating that after randomization safety and efficacy follow-up is performed in accordance with usual practice. A sizeable collection of safety and efficacy data was considered a precondition before a pre-market authorization pragmatic trial could proceed ethically. Nevertheless, it was expressed that—even in the presence of sufficient efficacy and safety data—patients might not always be called in for regular check-ups and adverse events may not be recorded accurately as follow-up is left to the treating physician:

> It seems that having commitments to safety monitoring, at an individual clinical level – like, that people come back with some frequency - and also at an aggregate level through data safety monitoring, is really important… To say the obvious, you are dealing with real people who have real medical needs, and if there are alternatives available that are not what is being tested in the trial, we absolutely need to be responsible for the welfare of the people in our trial, and keep track of their disease. (Bioethicist on pre-market authorization pragmatic trials)

Comparison with suboptimal usual care compromises clinical equipoise

Respondents expressed that pragmatic trials could become ethically challenging when they incorporate 'usual care' as a comparison group. Different interviewees referred to the SUPPORT study where the comparator arm (defined as 'usual care') consisted of a range of practices across a spectrum (84). Respondents stated that if usual medical practice is used as a comparator arm, it may expose subjects to less than optimal medical care.

A respondent within the pharmaceutical industry highlighted discussions with regulatory authorities about including usual care treatments in a randomized trial that were not believed to constitute the 'standard of care' due to either insufficient quality of the treatments or their suboptimal delivery. The respondent also expressed the view that choosing a comparator that lacks quality would make the trial results less informative:

> The aim of a pragmatic trial is to record what is happening in real life, however you may experience that you cannot proceed ethically with a pragmatic study when routine care is delivered poorly. That is an issue we all have to think about. It is always a matter of finding a balance between the real world and a more controlled, closely monitored setting in an explanatory sense. (Pharmaceutical Industry member with experience in clinical trial design and conduct)

Tailored or waived informed consent infringes patient autonomy

Respondents stated that the real world nature of pragmatic trials can be limited by additional requirements for research. If the informed consent procedure for a research intervention is more elaborate than the way consent is obtained for the same intervention in clinical practice, a pragmatic trial becomes less 'real world', as was voiced by different interviewees. Patients were said to behave differently if they are aware that they are participating in a trial (also known as the Hawthorne effect). In addition, the amount of paperwork and time needed to complete the informed consent procedure were experienced to impede recruitment.

Some clinical investigators and bioethicists believed the informed consent procedure for a pragmatic trial for marketed products could perhaps be tailored, though this would greatly depend on the particulars of the study:

> I think that there is no question that for an unapproved product you would always need informed consent, I don't want by implication to saying that for approved products that you never do. But I think that discussions can be on the table and can be looked at by a case to case basis, for a pragmatic trial for an approved product. (Bioethicist on the difference between pre- and post-market authorization pragmatic trials)

Respondents imagined that for some post-market authorization randomized research, informed consent perhaps could even be waived when the context would render it ethically acceptable. Justifications for waivers were named to be selection bias and limited generalizability of trial results. One bioethicist stated that, under certain specified circumstances, informed consent could be integrated into a routine clinic visit. A patient representative believed that when a patient's treating physician asks for informed consent for trial participation this would potentially endanger the patient's trust in receiving the best possible care from his or her physician. Another bioethicist questioned what waivers would exactly look like, either a complete waiver for informed consent or waivers for certain elements of the consent procedure.

Some interviewees expressed concerns that completely waiving informed consent would infringe patient autonomy as well as have a negative impact on patients' trust in biomedical

research. Some bioethicists stated that even if randomization would not meaningfully affect patients' clinical outcome, they may have a legitimate base for preferring one study arm over the other due to expected side effects or dosing scheme. Bioethicists occasionally felt that researchers proposed waivers of consent merely out of convenience:

> Whether waivers are justified in drug trials really depends on the risks people bear, whether standard of care is withheld, whether it really is reasonably impossible to obtain consent in large patient numbers as that is what is often argued… I mean, is that truly so impossible? And is it impossible because of the large patient numbers or because patients would be unnecessarily burdened by the consent procedure? There is a difference there… And I believe that we should be really critical in reviewing waivers to assess whether it is really impossible or whether the waiver just acts as an excuse for the sake of convenience. (Bioethicist on waivers of consent for post-market authorization pragmatic trials)

All interviewees expressed concerns for reducing informed consent requirements for unapproved products due to lack of real world experience and the presumed limited knowledge base in terms of safety and efficacy.

Minimal interference with real world practice drives arms to equivalence

According to some respondents, a pragmatic trial allows a considerable degree of physician flexibility with regards to altering patients' treatment while retaining them in the trial. Such flexibility was perceived to serve two ends: first, to ensure that patients enrolled in a pragmatic trial are treated optimally, and second, that a pragmatic trial remains as pragmatic as possible. This means that during a trial a patient can switch to an alternative treatment than the one he or she was initially randomized to, as would also be the case in real life. However, a clinical investigator had observed in a number of cases that allowing patients to switch in the course of their treatment inherently had driven the study arms to equivalence. In these cases, the intervention arm would then not separate from the comparator:

> I would like to emphasize again this problem of very pragmatic trials, which is the lack of separation [between arms]. Among all the [published] pragmatic clinical trials [in the literature] - there aren't that many of them compared to the number of RCTs done - but of the ones that are out there, I think only a couple out of maybe a dozen were able to differentiate the arms. Again, if you have confident physicians, intent-to-treat analytic approaches and a very pragmatic protocol, give it enough time, physicians doing what they typically do, will end up driving the arms to equivalence. (Pharmaceutical industry member on industry-sponsored pragmatic trials)

Different respondents commented on this phenomenon, saying that in designing a pragmatic trial efforts should be directed at ensuring that the trial results will be informative. Though respondents identified this issue as a predominantly operational challenge, we additionally label it an ethical one as respondents seem to imply that such trial results do not sufficiently contribute to science and society.

DISCUSSION

In this qualitative study we interviewed 34 stakeholders to identify the experienced and perceived ethical challenges related to (early) implementation of pragmatic clinical trials with pharmaceutical drugs. Design choices approximating real world conditions may be necessary to answer a pragmatic research question, yet have been shown to give rise to perceived ethical challenges in four domains: I) less controlled conditions creating safety concerns, II) comparison with suboptimal usual care compromising clinical equipoise, III) tailored or waivers of informed consent infringing patient autonomy, and IV) minimal interference with real world practice reducing the knowledge value of the results. The majority of the respondents believed real world evidence generation was valuable and necessary, however, pre-market authorization implementation of pragmatic trials was considered to increase ethical concerns as the investigational treatments would not have received regulatory approval yet.

The first challenge relates to the less-controlled, real world conditions in which a pragmatic trial is supposed to be conducted. Safety concerns were expressed about limited pre-trial data in pre-market authorization pragmatic trials, which exposes the underlying question of how much explanatory data needs to be available to control for risk of harm in more heterogeneous populations. Other concerns related to physicians' flexibility in delivering the test intervention in routine practice: lack of a detailed study protocol or lack of protocol adherence was questioned to adequately protect the safety of enrolled patients, more so in pragmatic trials before market authorization. These concerns raise questions about the duties and responsibilities of investigators: what should investigators do when they suspect or observe that some patients in the test arm are not receiving optimal medical care? Though safety concerns were expressed *within* a pragmatic trial, none of the interviewees mentioned patient safety in the absence of real world evidence *outside* a trial context. The current system moves from closely monitored trials to the use of new interventions in clinical practice with typically only minimal monitoring and limited, unstructured collection of safety data. Pragmatic trials could address this question of safety in routine care before allowing widespread use. One could thus argue that pragmatic trials are an important step towards increasing safe use of new drugs among the real world patient population and can be viewed as a strong ethical reason to perform such trials, particularly in situations where there is no efficacy or safety data comparing two comparable treatments.

The second challenge consists of determining whether it is justified to randomize patients to different treatment patterns used in practice, especially when the trial is conducted under real world conditions (supposedly with less control than in more traditional RCTs). It was questioned whether usual care ought to be submitted to randomized investigation when it consists of a range of treatments (each displaying a different risk-benefit profile) or when the treatment standard might be delivered suboptimally in the real world setting. Ethically, there must exist a state of clinical equipoise about the net preferred medical treatment prior to randomizing patients to different interventions (85), however, respondents echoed existing disputes about the adequacy of, or evidence base for, the interventions proposed for a trial. The ultimate goal of clinical trials is to meaningfully contribute to the understanding of different treatment effects,

to which usual care comparisons have proven challenging (86). Kass and colleagues state that "substantial evidence now points to the frequency and severity of the clinical harms that patients experience as a consequence of the medical errors and lack of supervision that occur in clinical care" (40). For Kass and colleagues, however, the problem of underprotection in clinical care acts as a powerful incentive to undertake improvement efforts such as comparative effectiveness research, directed at establishing which of two or more widely used treatments for the same indication works best for which patients.

Third, respondents acknowledged that informed consent procedures for post-market authorization pragmatic trials might not necessarily be as extensive as for pre-market authorization research. The more real life a trial is aspired to be, the less room there seems to be for obtaining trial-specific informed consent (in accordance with Good Clinical Practice guidelines), as was verbalized by respondents. Some investigators stated that the mere act of asking consent from patients interferes with real life conditions. In order to be able to judge to what extent research consent is truly intrusive, we remark that is important to have an accurate understanding of how consent is obtained for a specific intervention in clinical practice. In the literature, modified consent has been suggested for certain pragmatic trials (56, 76, 87). For some pragmatic trials with standard of care treatments, even waivers have been proposed (24, 55). These suggestions have sparked controversy which was paralleled in the interviews, displaying concerns of infringing patient autonomy.

Lastly, it was understood that if a patient or physician enrolled in a pragmatic trial prefers an alternative treatment to the one the patient was initially randomized to, the patient can be allowed to change treatments while staying in the study. Respondents experienced the switching between study arms to drive the arms to equivalence, which to some indicated that the trial results are less informative because the comparator does not separate from the test drug. However, one could argue that if no treatment effects are observed in a pragmatic trial that allows switching, this is the real life net effect—a finding that provides science and society valuable answers to what in reality has no added benefit. Grobbee and Hoes have observed that there is ample confusion about the nature of pragmatic trials. They state that "cross-over" from one treatment arm to the other can occur in both pragmatic *and* explanatory trials, and that this may not be problematic as long as patients are analyzed by means of *intention-to-treat* approaches (1). Moreover, *not* allowing patients to switch treatments could lead to a delay in optimal care for the individual patients enrolled as well as make patients less satisfied with the overall treatment they received. However, if many crossovers are expected sample size might need to be increased when the clinically meaningful difference is smaller than the expected difference based on perfect protocol adherence. The observed attitudes towards switching highlight the need to specify what the value is that pragmatic trial results hold for society and how their value can be optimized.

We note that this explorative, qualitative study had some limitations. The difficulty with addressing the issues of pragmatic trials *in general* is that the term 'pragmatic trial' refers to a range of RCTs across a continuum, each trial displaying different design features and each testing a different type of intervention (35). Due to the exploratory nature of our study we

did not narrow down towards respondents what we understood to be a pragmatic trial. Thus, stakeholders' implicit assumptions about design characteristics have likely influenced the ethical challenges foreseen. This means that for some pragmatic trials a raised challenge might be an issue, whereas in others it is not: e.g., detailed protocols have been observed in some trials that are self-described as pragmatic but in others they may be completely absent. From the interviews it also became clear that different, sometimes erroneous assumptions about a pragmatic trial were held. One respondent doubted whether a pragmatic trial entailed randomization or not. In addition, experiences, perceptions, opinions and speculation are ideally separated in the analysis; however, in practice this is difficult to do. Nevertheless, we believe our study provides some valuable insights into the ethical issues of (early) pragmatic trials and, in addition, exposes some persistent difficulties in the discourse about pragmatic trials in terms of their definition and design features.

Pragmatic clinical trials are welcomed as a valuable means to obtaining the type of high-quality scientific evidence that has the potential to directly enhance health care decision-making (10, 36). However, heated discussion still continues on when and how to do it, both practically and ethically. In a previous review of the literature, we found that different attitudes towards the moral relevance of the intertwinement of research and clinical care led to discussions about whether current clinical trial regulations are sufficient to protect the rights and interests of patients enrolled in pragmatic trials (78). We believe that the experiences and perceptions identified in this qualitative study provide an important base for improving our understanding of the ethical complexities of pragmatic trials and their potential implementation in the drug development process. Further work in terms of methodological analysis and ethical evaluation is needed to flesh out which concerns pose truly meaningful ethical challenges and which do not.

CONCLUSIONS

Recent collaborative initiatives are exploring ways to facilitate the (early) implementation of pragmatic trials in routine health care settings. To do so effectively and responsibly, the ethical challenges of pragmatic trials need to be identified and addressed. We performed a qualitative study among stakeholders in the field of drug research as a means to capture views of these challenges. With respect to pragmatic trials with pharmaceutical drugs, respondents perceived potential ethical challenges relating to the presumed lack of control, the use of routine care as a comparator, the need for modified informed consent and the power of a pragmatic trial to detect differences when crossover is allowed. We identified the related ethical challenges of risk assessment, evaluating the acceptability of usual care as a comparator and the tailoring of informed consent procedures as well as ensuring the trial results have knowledge value. Further exploration of these perceived concerns and challenges is key to grasping the ethically relevant features of the whole range of pragmatic trials, from their implementation in drug development to their use in post-market authorization research.

CHAPTER 4

PARTICIPANT ELIGIBILITY, RECRUITMENT AND RETENTION IN PRAGMATIC TRIALS

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ABSTRACT

This paper addresses challenges of identifying, enrolling and retaining participants in a randomized trial conducted within a routine care setting. All patients that are potential candidates for the treatments in routine clinical practice should be considered eligible for a pragmatic trial. To ensure generalizability, the recruited sample should have a similar distribution of the treatment effect modifiers as the target population. In practice this can be best achieved by including—within the selected sites—all patients without further selection. If relevant heterogeneity between subgroups is expected, increasing the relative proportion of the subgroup of patients in the heterogeneous trial could be considered (i.e., oversampling), or a separate trial in this subgroup can be planned; nevertheless, selection will occur. Low enrollment rates and loss to follow-up can introduce selection and can jeopardize validity as well as generalizability. Pragmatic trials are conducted in clinical practice rather than in a dedicated research setting, which could reduce recruitment rates. However, if a trial poses minimal burden to physicians and patients, and routine clinical practice is maximally adhered to, the participation rate might be high and loss to follow-up will not pose a specific problem to pragmatic trials.

INTRODUCTION

Pragmatic trials compare the effectiveness of an intervention in a randomized study under real world conditions, both to identify the optimal treatment for individual patients and to inform health care professionals, payers and the general public about the effects of treatments for patients in day-to-day clinical practice (13, 88).

Explanatory trials often include highly selected, 'ideal' patients, with the aim of showing maximal treatment effects with minimal adverse effects and/or minimizing the required number of patients to obtain the results. The included patients may, however, not be comparable to real world patients with respect to relevant treatment effect modifiers, like comorbidity, disease severity and risk factors (89). As a consequence, the generalizability of the study findings to a setting with diverse patients, practices and conditions might be limited or uncertain. Pragmatic trials, on the other hand, adopt more lenient eligibility criteria that reflect the diversity of patients that are treated in routine clinical practice.

Pragmatic trials aim to investigate the effectiveness of a treatment delivered under routine care conditions to all those eligible for receiving treatment. Although there will be no deliberate selection in pragmatic trials, the act of enrolling in a trial will invariably lead to at least some selection (90). We need to be aware that patients who consent to a trial may differ from those who do not, which may compromise generalizability of the results (89). Low recruitment rates not only increase the duration and costs of a trial, they may also hamper a sufficiently large sample size, thereby impeding correct inference. After patients have consented to participate, it is key to retain them in the trial until the endpoints have occurred to prevent (selective) loss to follow-up. In this paper, we discuss challenges and solutions of identifying, recruiting and retaining participants in pragmatic trials, guided by three questions: I) who should be eligible for the trial; II) who actually enters the trial, and III) who stays in the trial until completion?

WHO SHOULD BE ELIGIBLE FOR THE TRIAL?

Characteristics of the study population

Specific characteristics of a selected patient group can modify the nature and magnitude of an intervention effect; this is called effect modification or heterogeneity of treatment effects. In the pragmatic STAR*D study, only 22% of the enrolled patients met the inclusion criteria commonly applied in phase III explanatory clinical trials for depression. The patients that met these stringent inclusion criteria had a shorter illness duration, tolerated the test drug better and had a higher response to the treatment compared to the patients not fulfilling these criteria (91). In another study, the efficacy of the newer generation antidepressant escitalopram was shown to be higher in patients with severe depression compared to patients with milder depression (92). There are other examples of factors that are known to influence drug efficacy and adverse events. In patients with a suspected diagnosis, the magnitude of the treatment response may be smaller than in patients with a confirmed diagnosis. In elderly patients, age dependent changes in metabolism and comorbidities may affect drug efficacy or adverse events (93). Participants' behavior could also modify the effect of a drug, for example when drug adherence is promoted.

Ideally, the patients to be enrolled in the trial are (as a group) representative of the target population in terms of all factors—both known and unknown—that may modify the treatment effect. Some degree of effect modification can be expected in almost all studies. While randomization in trials controls for (un)known confounding, random sampling takes care of unknown effect modification, since it is expected to result in a group of patients that is representative in terms of (un)known effect modifiers. Although the aim is random sampling, in practice random sampling is hardly ever done. Random sampling is approximated by including (in the selected sites) all patients without further selection. Despite such efforts, in practice those enrolled in the trial may not comprise a random sample of the target population. Particularly in pre-market trials, it might be difficult to fully characterize the patient group that will actually receive the treatment in practice. Broad eligibility criteria are likely to lead to a trial population that is more representative of future heterogeneous patient populations compared to more stringent eligibility criteria.

Defining eligibility

A pragmatic trial should include a sample of all patients that are indicated for the treatment in routine clinical care, without further interference or selection to maximize the generalizability of the trial results to the target population (3). The number of exclusion criteria should be kept to a minimum. Patients should be selected based on their true indication of interest, defining the target population. Obviously, as goes for all clinical trials, patients with absolute contra-indications should be excluded from participation. Patients should not be selected on their expected drug adherence, practical difficulties or compliance. The International Conference on Harmonisation (ICH) guidelines generally advise against the enrollment of patients in multiple clinical trials, though the reasons why already enrolled patients should not be eligible are not addressed (94). In the literature, concerns about co-enrollment typically relate to patient safety, scientific validity and burden for the patient (95). These concerns are more evident in earlier phase, explanatory trials than in pragmatic trials with approved interventions. The ICH guidelines do leave some room for justified exceptions; co-enrollment in some post-market pragmatic trials might be acceptable, which is also a common practice in specific countries or disease areas (96). Allowing co-enrollment holds potential to overcome the problem of underrepresentation of particular patient groups, who tend to be eligible for multiple trials, usually because they have multiple comorbidities. Enrollment in multiple trials also enables patients to access different (innovative) therapeutic interventions at the same time, and it could enhance trial enrollment. However, multiple inclusion could potentially affect the power of the trial; if the intervention tested in both trials influences the primary outcome, the event rate of the primary outcome could be influenced (97). Wider inclusion criteria as used in pragmatic trials probably lead to more variability in the response to treatment and, in case of continuous outcomes, may consequently require a larger sample size.

Vulnerable or special populations

The purposive inclusion of participants in whom the intervention may act differently leads to a broad range of patients to be enrolled in a pragmatic trial. This raises the issue of eligibility of

vulnerable or special populations, such as children, pregnant women and their unborn fetuses, and persons with physical handicaps or mental disabilities. Vulnerable groups have traditionally been excluded from clinical trials as they are less capable to protect their own interests. However, systematic exclusion from pragmatic trials prohibits our understanding of the real world benefits and harms of drugs used by these groups. For example, in the US about two out of three pregnant women use prescription medication, many of which the effectiveness and safety has not been investigated during pregnancy, as pregnant women are generally excluded from clinical trials (98).

Belonging to a vulnerable population should in itself not be a criterion for exclusion from a pragmatic trial, in order to allow for equitable access to knowledge obtained through research. Enabling these groups to participate in pragmatic trials with novel interventions offers the additional benefit of access to a potentially advantageous treatment. Responsible inclusion of vulnerable persons in a pragmatic trial is nowadays encouraged, if additional protections are secured where deemed necessary based on expected risks, effects and population characteristics (71, 77). A more stringent justification of the inclusion of vulnerable persons is needed in a pre-market setting, where less evidence is available on the safety of new treatments.

If there are vulnerable patients for whom the effects of treatment are hypothesized to diverge from the overall trial result, a trial of sufficient size in this specific subgroup could be planned at a stage when more data is available on safety in the population, to balance the value of including vulnerable persons against the risks and additional efforts. However, this approach is resource intensive, and since resources tend to be limited it might result in trials taking years to be planned, if at all feasible. Alternatively, one could increase the relative proportion of vulnerable patients in the heterogeneous trial (a method called oversampling) to obtain (more) meaningful results that allow to test for (absence of) interactions. Also, a pooled analysis of multiple trials could be performed to clarify differential effects in specific patient groups (99). This would be particularly suitable if large differences are anticipated.

Subgroups

The more liberal inclusion criteria as generally applied in pragmatic trials are intended to result in a heterogeneous study population. The trial overall will show results that pertain to the real world target population, including its representative subgroups. If it is demonstrated that the treatment works in all kinds of patients and under a variety of conditions, it could be likely that the treatment works in typical patients seen in everyday practice.

A pragmatic trial enables exploration of the consistency of the effect in different subgroups. However, subgroup analyses in general remain a topic of debate. When looking at subgroups—which are often relatively small and underpowered—relevant group differences may remain undetected. At the same time, due to chance finding, differences may be detected which do not exist in the aggregate population. Current opinions vary from always using the overall effect, whatever subgroup effect is of interest or whatever effect expected, to encouraging subgroup analyses based on well-defined hypotheses, amongst others for reasons of equity (99, 100). As a potential bridge between these extremes, approaches that shrink the subgroup treatment estimates towards the average treatment effect across all participants could be

considered (101-103). Subgroup analyses may also help to explain differences between the results obtained in a pragmatic trial and an explanatory trial that have compared identical interventions. If the results from explanatory and pragmatic trials yield discordant results, it may be—amongst other reasons—because the therapy works in some patients and not in others, and the patient mix in these trials is different. Analytic strategies to optimize the value of pragmatic trials for the diversity of patients, such as individual patient data meta-analysis, merit further attention.

WHO ACTUALLY ENTERS THE TRIAL?

Even though the goal is to recruit all patients that might have an interest in the treatments evaluated by a particular pragmatic trial, selection will nevertheless occur. Only a proportion of eligible subjects will actually enter the trial.

Selection can occur both at the level of the health care professional and the patient. First, health care professionals might not join the trial; and even if they join, not all their eligible patients may be invited for the trial. If invited, patients may decide not to participate. This may ultimately lead to a group of patients that respond differently to the intervention compared to the targeted population. Treatment response might also change due to unintended consequences of the pre-randomization process—assessing eligibility, providing study information and signing informed consent (104, 105). This may affect generalizability as extrapolation of the trial findings to future users of the drug may be limited, and it could result in a biased effect estimate. How much selection takes place may vary between countries, health professionals, patient populations and disease areas.

Many trials face challenges with recruitment of a sufficient number of participants (90). For pragmatic trials, specifically, this might be an issue as the trial is conducted in a routine care setting, where health professionals may be less experienced in, and have fewer resources dedicated to recruiting subjects for trials, as opposed to a more experienced and dedicated research setting (49, 106). On the other hand, trials that are embedded in routine care—thus requiring limited additional activities—pose fewer barriers for health care professionals and patients to participate.

Below we will discuss the factors influencing enrollment of participants in pragmatic trials. We start from the point where health professionals select their patients. It should be noted that strategies aiming at improving recruitment could also introduce selection, if targeted at or invoking a response from a specific subpopulation.

Strategies for identifying and approaching eligible patients

The way eligible patients are approached for participation influences the selection of patients enrolled in a randomized trial. For a clinical condition, the most pragmatic approach would be to recruit patients with an indication for the treatment as they present themselves in routine care, without further interference or selection (3). This is also known as 'point-of-care' randomization. When employing point-of-care randomization, health care professionals

should be attentive to inviting their patients for participation during a routine patient visit, and must have sufficient time for and knowledge about the study to adequately inform potential participants (107). Pop-up menus embedded in the electronic health record can help to alert a health care professional that a particular patient is eligible (49). Approaching patients for participation through their trusted health care provider can improve enrollment rates, with minimal disruption to usual care conditions. If necessary, dedicated study staff may be employed to overcome operational challenges concerning recruitment during a routine visit.

Practitioner databases or electronic health records can also be used to select eligible patients with a chronic condition. These patients could be invited to the health care facility via e-mail, or they could be informed about the study while they are in the waiting room for a regular visit. Direct contact in the waiting room has been shown to improve participation rates, but was nevertheless considered less effective than a mail-out (108). Accessing electronic patient information or contacting patients are widely reported challenges for recruitment through databases (109). Another means to enhance recruitment is to directly call on participants through newspaper advertisements or social media, although this method might also end up recruiting a selected group of patients.

Patients or disease under study

The more lenient inclusion criteria as applied in pragmatic trials may increase the number of eligible patients and reduce efforts required for screening potential eligible patients. Health care professionals may nevertheless have their own reasons for not inviting a patient for a trial, based on certain patient or disease characteristics. For example, patients might not be invited because of expected practical or language difficulties or due to concerns for the elderly participant (110, 111). The risk of reduced generalizability in this way could be minimized by ensuring that the study protocol shows maximal resemblance with day-to-day clinical practice, and by encouraging health care professionals to invite all eligible participants.

Unfamiliarity with clinical research

Many of the barriers to participation in clinical research relate to the fact that patients are generally unaware that clinical research is required to improve patient care. This lack of awareness can lead to doubts or misunderstanding about the study's intent, which might make patients reluctant to participate in a trial (112). Patients report feelings of distrust towards researchers and discomfort with the trial setting, a computer "deciding their fate" (i.e., randomly allocating treatment), or the research process in general (111, 113). Patients often feel unable to decide whether to participate, generally resulting in non-participation (114). A strict and elaborate informed consent procedure could increase these feelings of distrust, and these feelings might be even stronger when the trial is conducted before the drug is licensed, as often less is known about potential (long term or rare) side effects. The rationale, methods and the potential benefits of the study should always be explained clearly (49). Involving patient representatives at an early stage may help improve the content of the information and modes of communication (115).

Health care professionals, patients and the general public could be reminded that clinical research aims to improve the quality of health care services—such reminders could be emitted through media campaigns, for example. If the opportunity to participate arises, the principles of research will already be more familiar and patients may be more likely to engage (116). Professional treatment guidelines could incorporate the possibility of mentioning any ongoing pragmatic trial in the field, to provide patients the opportunity of combining adequate treatment with systematic knowledge generation. Patients should be explicitly informed that the decision whether or not to participate will not affect their relationship with their health care professional (59). Emphasizing that treatment by their trusted health care professional will be continued in either study group may improve the perception of the research process.

Study design and treatment groups

In general, pragmatic trials are not blinded so participants will know which treatment they are receiving. Such open label research designs have been shown to increase recruitment rates (117). A randomized design, on the other hand, is often viewed as a barrier for trial participation since patients do not have the option to choose for a preferred intervention (111, 113).

Alterations to the randomization process have therefore been proposed. The timing of the intervention is randomized in a stepped-wedge design. In a Zelen's design, patients are invited to participate conditionally upon treatment, as randomization is performed beforehand. Another method is cluster randomization, where a particular treatment is randomly allocated to an entire research site.

Other barriers to participation in clinical trials are the presence of a no-treatment group, fear for potential side effects and a strongly protocolled manner in which interventions are delivered (111). Pragmatic trials reflect usual clinical practice and typically have a less complex and stringent study protocol. In addition, more is known about potential side effects of the compared interventions, which could improve patient participation (49). Also, availability and access to a treatment that is unavailable to patients outside the study could positively influence the participation rate (112). Whereas in post-launch, standard of care pragmatic trials both interventions are typically available to patients outside the trial, the exclusive availability of a treatment in a trial might constitute an incentive for participation in a pre-launch or peri-launch pragmatic trial.

Practical aspects of trial participation

Conducting clinical trials generally demands additional time and efforts from both patients and physicians. Minimizing the administrative burden will positively affect the number of patients invited for a trial. To identify and overcome barriers for health care professionals, a priori qualitative methods can be useful (118). Practical barriers to participation by specific patient groups should be identified and addressed before starting a trial, such as time and costs required to travel, hearing impairments in the elderly, arrangement of day care for children of young parents, or time schedules that do not interfere with school hours for children (115, 119). If

routine clinical practice is respected without additional follow-up visits, these practical aspects are expected to be of minor influence.

Another frequently mentioned barrier to recruitment— both by physicians and patients— is an extensive and time consuming informed consent procedure. Modifications that shorten the informed consent procedure have been proposed to better reflect real world conditions and to enhance recruitment (76). Engaging patients in the design of the informed consent procedure and the patient information form may lead to greater public support for such modifications.

Based on recent examples, the Clinical Trials Transformation Initiative Working Group recommends the engagement of all stakeholders early in the trial development process in order to improve recruitment, although the magnitude of the improvement is still unclear (16, 120, 121).

WHO STAYS IN THE TRIAL?

After patients have been successfully selected and enrolled, the final challenge is to retain them in the trial until the outcome of interest occurs. If loss to follow-up is random, it will reduce the statistical power to detect group differences but it will not bias the results. If loss to follow-up is differential such that it leads to incomparability of randomized groups, this could introduce bias. Bias could be introduced when (explanatory) trial elements are added to only one arm of the trial; for example, this occurs when only patients in the test arm are called back for to follow-up visits or when trial medication is provided free of charge exclusively to those patients randomized to the test arm (122).

Since pragmatic trials are embedded in routine clinical practice, typically without any additional visits and without use of placebo, the attrition of subjects is expected to be low, especially if the outcome measures are extracted from electronic medical records. However, safety data is often not recorded in sufficient detail in the electronic health record. Additional safety data collection thus may increase the burden of participation during the study compared to usual practice. This might be the case especially for pre-launch trials where little is known about the safety profile. Furthermore, the behavior of patients in a trial can be influenced by awareness of being observed, which is an expression of the Hawthorne effect—although the magnitude of such effects is unknown and unpredictable (123). To maximize generalizability of the findings to the target population outside a pragmatic trial, the feeling of being observed in the trial should be minimized. This can be achieved, amongst others, through minimal disruption to patient-physician encounters in routine practice, aligning informed consent with usual care, and by minimizing baseline data collection and measurements (104).

CONCLUSION

In order to achieve their goals, pragmatic trials should be aligned with clinical practice as much as possible—all patients that might receive the drug in clinical practice should be considered

eligible, with minimization of additional research-related activities and procedures. Enhancing recruitment rates will increase the operational feasibility of a pragmatic trial as well as improve the generalizability of the trial results. Engagement with patient representatives and health care professionals provides valuable input during study development to ensure alignment with routine care and helps identify potential barriers to participation early in the design process.

CHAPTER 5

CHALLENGES OF INFORMED CONSENT FOR PRAGMATIC TRIALS

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ABSTRACT

The Innovative Medicines Initiative's (IMI) GetReal consortium aims to develop strategies to incorporate real world evidence earlier into the drug life cycle to better inform health care decision-makers on the comparative risks and benefits of new drugs. A series of eight papers in the *Journal of Clinical Epidemiology* evaluates the operational challenges in designing and conducting pragmatic trials and the impact of certain design features on validity, generalizability, precision and ethical acceptability. The traditional consent model for randomized clinical trials has been argued to pose substantial hurdles to the practicability of pragmatic trials: it would lead to recruitment difficulties, reduced generalizability of the results and selection bias. The present paper analyzes these challenges and discusses four proposed alternative informed consent procedures and their ethical implications.

INTRODUCTION

Pragmatic trials hold potential to deliver the high-quality scientific evidence needed to guide health care decision-making by regulatory bodies, medical practitioners and health technology assessment (HTA) agencies (3, 36, 43). Traditionally, explanatory randomized controlled trials (RCTs) have served as the main source of clinical evidence supporting market authorization decisions of new drugs. However, due to differences in use and users of drugs as tested in explanatory trials versus those as prescribed in the real world, a so-called knowledge gap between drug efficacy and effectiveness has arisen (4). Whereas explanatory trials aim to obtain knowledge about the biological effects of new drugs in highly standardized and idealized settings, pragmatic trials collect real world comparative effectiveness data in patients that are treated in routine clinical practice (10, 13). The term 'pragmatic trial' is typically used to refer to randomized trials comparing different routine care interventions, though it is now acknowledged that pragmatic trials can also be conducted in earlier stages of the drug life cycle with new interventions. As such, the Innovative Medicines Initiative's (IMI) GetReal consortium explores ways to implement pragmatic trials earlier into the process of drug development and evaluation (8).

For all pragmatic trials, whether in earlier or later stages, a significant challenge is to preserve the real world nature of the trial. Some have raised the concern that current ethical trial regulations compromise that character, such as the requirement to obtain extensive, written, prospective informed consent (49, 124). Discourse concentrates on the question whether all traditional requirements for informed consent for RCTs are ethically necessary to sufficiently protect the rights and interests of participants in a pragmatic trial. Moreover, it has been argued that certain requirements are so restrictive that some pragmatic trials become impossible to conduct (39, 76, 87). This paper first analyzes claims about the challenges that traditional informed consent procedures might pose to the practicability of pragmatic trials. Subsequently, the paper discusses four alternative informed consent procedures proposed in response to these claims. Before considering alternative consent models, we conclude that it is important to provide compelling arguments why a particular pragmatic trial becomes impracticable with traditional consent requirements. The relative impracticability needs to be weighed against the implications of reducing the degree of transparency and limiting patients' freedom of choice regarding treatment options.

TRADITIONAL REQUIREMENTS FOR INFORMED CONSENT

Informed consent is based on the principle that competent individuals have a right to choose freely whether to participate in research. Enshrined in the Declaration of Helsinki, the obligation to obtain informed consent protects the individual's freedom of choice and respects the individual's autonomy (70, 71). Many guidelines and regulations for clinical trials in Europe have incorporated the duty to seek written, prospective informed consent from research participants, such as the International Conference on Harmonisation (ICH) Good Clinical

Practice guidelines (125) and the European Clinical Trials Directive (2001/20/EC) (126). To ensure valid, voluntary informed consent for clinical trials involving medicinal products, these trial regulations require that potential participants are informed about the purpose of the study, the fact that it constitutes scientific research, the potential risks and benefits, the trial's procedures, and that participants can withdraw at any time during the study without consequences. In addition, researchers must ensure that the potential participant has understood the information and has decided on participation without having been subjected to coercion or undue influence (70, 71). Recently approved amendments to the European Directive state that only one type of trial may be exempt from the consent requirements: cluster RCTs in which groups of subjects rather than individual subjects are allocated to receive different approved medicinal products may make use of simplified means to obtain informed consent (127). Necessary conditions are that there are no interventions other than the standard treatments and that the protocol justifies the reasons for obtaining consent by simplified means. The trial should also classify as a 'low-intervention' trial indicating use of approved products in accordance with the marketing authorization and with minimal risk or burden from additional diagnostic or monitoring procedures. The 2012 Ottawa Statement presents similar conditions for a waiver or alteration of informed consent for cluster RCTs, knowingly, that the research is not feasible without modified consent, and that the research-related procedures do not pose more than minimal risk (128). Pragmatic trials that randomize individual participants or that investigate unapproved products are still required to obtain full or 'traditional' informed consent from participants.

CHALLENGES TO THE PRACTICABILITY OF PRAGMATIC TRIALS

The traditional requirements for informed consent have raised issues with respect to the practicability of the research (78). Considerable loss of real world features diminishes the value of a pragmatic trial as generalizability of the results to usual practice is a key aim, which in turn begs the question whether the trial is worth doing at all. If the research question cannot be satisfactorily answered due to consent requirements, the trial becomes 'impracticable' (129, 130). Traditional informed consent procedures are believed to make pragmatic trials impracticable if they lead to low enrollment, and a study sample that is not representative of the real world patient population (39, 43, 76, 87).

With respect to enrollment challenges, reluctance of physicians towards spending time on consent procedures has been described as an important factor for trials failing to reach patient recruitment targets (49, 90, 111). General practitioners report that obtaining informed consent for a pragmatic trial during a regular consultation would probably not be feasible even if they believed the study was worth doing (49). It has been argued that the requirements for informed consent and regulatory oversight for clinical trials in general are time consuming and expensive, and may be disproportionate for pragmatic trials that compare routine care interventions that have "already been shown to be safe and are in widespread and routine use" (44).

Regarding the challenge of obtaining reliable and generalizable data, lengthy consent forms have been argued to deter specific groups of patients from participating in a clinical trial. Non-participation for this reason could be due to time constraints, overestimation of the study risks or any other kind of misunderstanding of the provided information (111, 131). As a result, standard consent might lead to selection and the underrepresentation of particular groups of patients. If, for example, patients of lower socio-economic status or sicker patients are less likely to consent, the trial results will be less applicable to the more heterogeneous real world population. This selection might lead to an effect estimate that is not generalizable to the broader population as defined by the initial inclusion criteria (39, 43, 87). It has also been suggested that once patients are enrolled in a trial their behavior might be affected by awareness of being observed. Such phenomena (described as the Hawthorne effect) are still poorly understood (123), but have led some to believe that the more elaborate an informed consent procedure is—or in other words, the more it deviates from how treatments are prescribed in real life—the less generalizable the trial findings will be to the real world (132).

EXAMINING THE IMPRACTICABILITY ARGUMENT

The first issue that needs to be addressed is whether an informed consent procedure actually leads to impracticability, and next if proposed alternatives are ethically justifiable and effective. Impracticability in terms of pragmatic trials tends to refer to a compromise on real world features that makes it (almost) impossible to answer the research question. This can be due to limited generalizability, low recruitment rates and/or selection bias.

It seems that the issue of reduced generalizability can emerge due to the mere act of asking consent or through the mode of recruitment (e.g., lengthy forms or time-consuming procedures). If eligible patients decline study participation because of reasons that are intrinsic to the purpose of informed consent (e.g., because patients do not wish to change their current therapy), alterations to traditional consent procedures are never defensible. Only if refusing participation is due to practical reasons that are extrinsic to the purpose of informed consent (e.g., physicians do not have time for consent procedures), altering traditional consent could be an ethically defensible solution. Such reasons may allow for leaving out some of the traditionally required information to approach real world conditions and to enhance comprehensibility of the forms.

Still, 'true' impracticability may be dependent on the availability of options to enhance recruitment. To what extent deviations from real world practice are acceptable is a matter of degree. Therefore, some compromise on real world conditions might be acceptable if it means increasing the number of enrolled patients. If physicians are the limiting factor due to time constraints, economic resources provided by the sponsor could be used to reimburse physicians for time spent on consent procedures during clinic hours or to contract study nurses to take on part of the workload. The pre-market pragmatic Salford Lung Study used these strategies, and an interim publication during the conduct of the trial discussing the study design and proceedings did not suggest that consent procedures made the study impossible (25).

In most pragmatic trials, traditional informed consent will not make the trial inherently impossible. Rather, consent requirements can reduce the real world character and thereby the applicability of the results. In addition, these requirements may reduce the participation rate and increase the duration of the trial due to the time needed for obtaining traditional informed consent. The degree to which these challenges lead to actual impracticability will depend on the particulars of a specific pragmatic trial. For example, a good match between trial consent and consent in the real world may not always be strictly necessary to ensure high generalizability; only if consent is a relevant modifier of the treatment response will such a match be required (133). However, in a number of cases it will remain unclear to what extent informed consent procedures actually affect treatment outcomes. The notion that a more detailed consent process will make a participant behave differently throughout the trial seems to overrate the power of the potential of the consent process to affect patient behavior and outcome. In addition, for some pragmatic trials, obtaining traditional informed consent during a clinical encounter might not be as burdensome as initially believed. Physicians enrolled in the pragmatic eLung study reported that the consent process usually took 5 minutes and was feasible on most occasions (49). As such, the only way of evaluating whether there are legitimate reasons for a pragmatic trial's impracticability is by carefully examining the claims why this exactly would be the case.

PROPOSED ALTERNATIVES TO TRADITIONAL INFORMED CONSENT

Scrutinizing claims about impracticability is important since if they turn out to be invalid, no alternative means of obtaining informed consent is required—let alone ethically justified. To put it differently, alternative consent models for pragmatic trials require justification. The impracticability of the research is not a sufficient justification, but at least a necessary condition. Another necessary condition almost always related to the permissibility of consent modifications, but which we will not discuss here, is that the research does not pose more than minimal risk (24, 60, 134). A number of alternatives for traditional informed consent have been recently proposed for pragmatic trials that compare therapies that have already been incorporated in clinical practice (76). These alternatives all have the objective of providing patients the information they consider relevant to their decision-making while better integrating the consent procedure within routine clinical care to overcome the challenges as discussed.

Integrated consent

The integrated consent model is targeted at pragmatic trials comparing commonly used treatments in routine practice which "have been independently validated through well-controlled clinical trials" and which in practice only require verbal consent (56). The model proposes an approach that integrates clinical and research consent within the same clinical encounter. The patient's treating physician will discuss the treatment's rationale, the alternatives, the use of randomization and the potential harms and benefits of the compared treatments. The patient can then opt-in through oral or written consent. The physician documents the conversation

and its result in the patient's electronic health record, and proceeds with the care that he or she would normally deliver in the context of clinical practice.

Targeted consent

The targeted consent model is proposed to avoid selection bias and minimize interference with clinical care when standard of care treatments are compared (87). The model requires providing potential participants only the following information additional to the information that would be conveyed if the intervention was provided outside the trial: the fact that enrollment involves patients helping investigators to evaluate the treatments under study as well as all the added, research-related risks. By providing this additional information, the patient can decide for herself whether or not to enroll. The targeted consent model consists of a verbal disclosure accompanied by a written consent form repeating the verbally disclosed information and describing the following: I) procedures and duration, II) instructions on taking the medication, III) availability of the investigational treatments to patients outside the research setting, IV) confidentiality measures, V) contact information and VI) a statement that the patient is free to decline research participation and to stop participation at any time without consequences. A substantial difference with the integrated consent model is that during targeted consent the patient is not informed about the randomization process.

Broadcast approach

The broadcast approach makes use of general notifications placed in prominent locations, informing patients that they could (continuously) be part of comparative effectiveness research with standard of care interventions (potentially pragmatic trials) (24, 47). This approach allows patients to ask questions about their participation, and if there is no option for non-participation at their care facility, they can decide to seek care elsewhere (76). It is believed that as long as the trial is implemented in a health care context where patients are regularly informed that randomized research involving minimal risk is occasionally permitted to take place, no express informed consent is ethically obligatory (24).

Waivers of consent

A waiver of consent means that participants are not informed about the research and that they do not actively decide on whether or not to participate (76). In Europe and in the United States, consent waivers for RCTs are currently only permitted under highly restricted circumstances, which are likely to exclude most pragmatic trials from consent exemptions (66, 125, 126, 135). Nevertheless, Truog and colleagues have argued in favor of consent waivers for pragmatic trials in which (I) all treatments offered in the trial may be offered outside the trial without specific informed consent, (II) treatments do not involve more than minimal additional risk in comparison with any of the alternatives, (III) genuine clinical equipoise exists among the treatments and (IV) no reasonable person should have a preference for one treatment over another (55).

IMPLICATIONS OF CONSENT ALTERATIONS

If a claim about a pragmatic trial's impracticability with traditional informed consent can be substantiated, alternative models might be considered. However, such alternatives will still need to be accounted for in ethical terms.

The integrated consent model maximizes transparency between physicians and patients, who are informed about all relevant aspects of the study. The model acknowledges that even if no a priori quantitative differences exist in the risks and benefits of the compared treatments, it is important to respect preferences and values that are meaningful to individual patients. Kim and Miller judge that "bypassing a person's agency—unless the person is incapable or not reasonably accessible—even for that person's own good is unacceptable" (56). These authors stress the importance of maximizing the degree to which the principle of respect for persons is respected: "[a]ny permissible alternative to regulatory consent should use procedures that preserve the greatest degree of respect for persons that is compatible with the practicability of the research" (129).

Targeted consent is designed to avoid the tension that waivers on the one hand, and traditional informed consent on the other, create. An important difference with the integrated consent model is the non-disclosure of randomization. Wendler does not explain why non-disclosure is necessary or desirable but he does provide an answer to possible objections to it: "[S]tudies indicate that when the existing data do not suggest that one intervention is better, randomization does not increase risks, suggesting that for the purpose of protecting subjects from harm, pragmatic trials do not need to disclose randomization" (87). This response suggests the underlying assumption that disclosure of randomization may hamper recruitment or affect the outcome of a trial in some way. It remains unclear, however, what physicians are supposed to answer when patients ask about the allocation method.

With regard to the matter of respect for patients, Wendler does concede that when the risks of the available treatments differ in ways that most individuals consider important, these differences should be disclosed (in line with the integrated consent model), after which the individual should be provided the opportunity to discuss any questions or concerns that they may have. At the heart of the discussion between the integrated consent model and targeted consent is the moral significance of the preferences of some potential participants (who regard some differences between the treatments as important while the possible differences in risks are not material or backed up by sufficient scientific evidence) in relation to those of the majority or the random patient (136).

Broadcast consent appeals to the sense of duty on the side of patients to engage in health-related research. In this model, anticipated societal benefits of research seem to be able to justify deviations from the traditional research ethics paradigm. Ruth Faden and Nancy Kass frame this model in terms of justice: present-day patients benefit from clinical research performed among patients in the past, which appears to justify—at least to some extent—a more general moral duty to contribute to research (41). Broadcast consent has the advantage of prior notification so patients can seek treatment elsewhere if they do not wish to partake in ongoing research

activities. Still, there is limited opportunity to object to participation as changing treatment practices can be burdensome. The model of broadcast consent may thus disproportionately burden vulnerable groups, such as impoverished or elderly patients. Furthermore, selection can occur if changing care facilities is less of an option for some patient groups compared to others. Complete waivers of consent, at the end of the 'consent spectrum' remove individual choice completely and imply not only a strong moral duty on patients to participate in research but also suggest superiority of the purpose of the research as serving the common good.

Transparency to the public is vital for trials as to secure patients' trust in not only the whole enterprise of biomedical research but also in clinical care itself. A recent qualitative study provided some preliminary evidence that relevant stakeholders find alternatives to traditional informed consent acceptable for low-risk pragmatic trials investigating widely-used therapies, as long as a sufficient amount of choice is preserved (137). Results from a recent survey among the US public (n=2130) about their views on alternatives to written consent for low-risk pragmatic trials investigating different standards of care showed that most respondents recommended written informed consent for trial participation, despite the fact that they acknowledged the value of the presented trial scenario and believed the trial did not pose additional risks (138).

DISCUSSION AND CONCLUSION

Alternative consent models for pragmatic trials have ethical implications that warrant assessment of the validity of the claims about a pragmatic trial's impracticability with traditional consent requirements in place. Traditional consent procedures have been said to diminish recruitment numbers and lead to unrepresentative samples, limiting generalizability to the population outside the trial and introducing selection bias. Proposed alternatives for consent procedures aim at overcoming these challenges while at the same time providing patients all the relevant information they need in order to make informed decisions. Each consent model, however, relies on different attitudes towards the principle of respect for persons and the related duty to inform patients, and represents different views on whether the common good entails particular patient duties to engage in clinical research. Especially consent waivers and broadcast notifications imply strong duties on the side of patients and a high social value of the research.

These four models were selected from the literature as they provided the most procedural detail. We acknowledge that this list is not exhaustive and that other viable alternatives, such as a simple opt-out, are not discussed. However, our objective in this paper was not to argue which model should be preferred for pragmatic trials, but to show that deviations from traditional consent have ethical implications that need to be balanced. The relative impracticability needs to be weighed against these ethical implications. In order to adequately perform such an evaluation, it is essential to expose the reasons why traditional consent would affect a particular pragmatic trial's practicability and to examine to what degree proposed alternatives affect patients' rights and could be actual solutions. Further work is needed to establish how a pragmatic trial's impracticability ought be balanced against the risks involved, along with other normative consequences of modifying traditional informed consent requirements.

CHAPTER 6

ETHICS OF INFORMED CONSENT FOR PRAGMATIC TRIALS WITH NEW INTERVENTIONS

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ABSTRACT

Pragmatic trials evaluate the comparative benefits, risks and burdens of health interventions in real world conditions. Such studies are now recognized as valuable to the peri-marketing 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 paper, we analyze the ethical issues of 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 would be ethical for EPTs by first identifying 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 applying those criteria to the pre-market and early post-market context. The analysis shows that neither waivers nor alterations of regulatory consent will be ethically permissible for pre-market EPTs. For post-market EPTs with newly approved interventions, waivers of consent will be ethically problematic but some studies might be ethically conducted with an alteration to regulatory consent.

INTRODUCTION

Pragmatic clinical trials are randomized controlled trials (RCTs) that compare treatments in routine or 'real world' health care settings to inform clinical decision-making (36, 43) and are designed in such a way that real world conditions are minimally interfered with (3, 13). Thus, real world designs typically aim to recruit a high number of patients attending clinics while minimizing disturbance to routine clinical work flow.

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 typically requires lengthy consent forms and procedures which significantly alter the routine work flow of 'real world' clinical settings and therefore compromises the pragmatic nature of the trial (41, 47, 56, 76, 87). Some have argued therefore that in some types of pragmatic RCTs where the risks are very low and patient expectations are not violated, the regulatory procedures of informed consent could be altered (56, 87) or even waived (24, 55).

Pragmatic trials are typically associated with standard of care comparisons, 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 in order to bridge the 'efficacy-effectiveness gap' (8). In this context, EPTs can study unapproved treatments in the pre-market phase (pre-market EPTs) as well as newly approved treatments in the early post-market phase (post-market EPTs).

Traditionally, pragmatic trials have not been attractive to commercial sponsors: there is considerable business risk in failing to prove comparative effectiveness at the expense of high trial costs (28, 29). And since pragmatic trial evidence is not required by regulators for market access nor explicitly required by reimbursement agencies, sponsors lack the incentive to design and conduct pragmatic trials. However, this landscape seems to be changing.

At least in Europe, there is a growing interest 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 (IQWiG), 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 (31). Also, in many European countries restricted reimbursement is given pending the outcome of post-marketing research. This requires a process, nevertheless, that may take a significant amount of time (months to even years) (33). Thus, EPTs that allow for direct, real world comparisons hold potential to bridge the efficacy-effectiveness gap and to reduce the time it takes for patients to gain access to new and effective drugs (2). Recently, the *New England Journal of Medicine* published results

from the first pre-market pragmatic phase IIIb comparative effectiveness trial, designed by the pharmaceutical company GSK in the field of chronic obstructive pulmonary disease (26). 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 research ethics regulatory requirements plays a central role. This paper explores the possibilities of introducing more pragmatism in pre-market (phase III) and post-market (early phase IV) clinical trials by analyzing the ethical issues surrounding informed consent for such trials. Specifically, we analyze whether modifications to traditional informed consent (which we refer to as 'regulatory consent' (129)) 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 pre-market EPTs and post-market EPTs and, importantly, also separate out the permissibility of alterations (e.g., simplified consent) versus full waivers of consent. We conclude that that there are salient differences between pragmatic trials, especially between pre-market EPTs and pragmatic trials with standard of care treatments, and delineate their implications for obligations to seek informed consent from patient participants.

A FRAMEWORK FOR ANALYZING ETHICS OF INFORMED CONSENT FOR EPTS

As noted, the rise of interest in standard of care pragmatic trials has led to a debate about if and how traditional regulatory consent might 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 (24, 56, 76, 87). Indeed, there have even been changes in some research regulations which explicitly accommodate 'simplified' procedures for consent for some types of pragmatic clinical trials. The recent amendments to the 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 (127). 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 using simplified means, in this case an opt out procedure for consent.

In the US, for studies that assess drugs as used in conformity with their market license some modification to regulatory consent might be possible if the following criteria are met: (I) the research involves minimal risk; (II) the science would be impracticable with regulatory consent; and (III) the rights and welfare of the subjects are not violated (66). There are good 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 (129). Commentators in the literature (41, 129, 130, 139) as well as EU and US regulations (66, 127, 135) broadly track the same conditions for modifications to regulatory consent procedures in clinical trials. 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, exactly how to determine whether a study adds 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 to their use in clinical practice (134, 140). Others have pointed out that such a broad definition ignores the significant range of research risks that fit the description of clinical trials that compare 'standard of care' practices (35). Faden and colleagues imply that a pragmatic trial can be deemed to pose minimal risk if "[t]here are few differences between the [market 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" (24).

Recently, a more systematic and formal approach to analyzing the research risks of standard of care pragmatic trials has been proposed (136). The approach shows that the research risks of standard of care pragmatic trials are minimal when one or both of the following conditions are met: (I) the ex-ante estimates of risks and benefits of the treatments to be compared in the trial are similar; and/or (II) the allocation ratios of treatments inside and outside the trial are similar. Since an EPT (either pre-market or post-market) compares 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 paper, the framework shows that an EPT can be considered to be minimal risk only if the treatments being compared can be regarded as having similar ex ante risk-benefit profiles (Table 6.1).

Impracticability

Another necessary condition for a modification of informed consent is that the trial would be impracticable if regulatory consent is required (44, 76, 130). Impracticability need not mean only 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, 'impracticable' will most likely refer to the latter. In this regard, commentators have pointed to specific challenges of regulatory consent pertaining to low recruitment rates (49) and selection bias and lack of generalizability to real world settings due to mandated use of non-routine (i.e., not part of the routine work flow of a clinic) procedures associated with regulatory consent (39, 43, 87). The primary threats to this particular type of impracticability relate to what we will label 'data

quality': the extent to which the data allow for 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 assess whether true impracticability exists we propose that three questions be asked (Table 6.1).

The first question aims to clarify the cause of the expected loss of quality of the trial results: Is the loss of data quality due to selection bias or inability to recruit a sufficient number of patients and can this loss be reasonably attributed to regulatory consent? 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 enrollment. 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 could be ethically problematic since the very point of informed consent is 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 due to time constraints (or the nurses in the clinic are also too busy, as it is not part of the routine work flow) or patients refuse enrollment because of the unexpected inconvenience of the informed consent process (111). If the reasons why patients do not enroll 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 then assesses the extent of the effect: Is the expected loss of data quality so extreme that the trial is not worth doing? This question carries by far the most weight for the impracticability assessment and requires some 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 due to regulatory consent 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 trial consent to the way consent for a treatment is obtained in the real world might not be strictly necessary to ensure high generalizability (133).

The third question explores the alternatives: Apart from modifying regulatory consent, are there no means or resources available that may be reasonably expected to counter the loss of data quality? There are two approaches to this problem: either more efforts are directed to recruitment procedures, such as reimbursing physicians for time spent on consent procedures, contracting study nurses to obtain informed consent or providing incentives to patients to compensate for the inconvenience, or 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 that patients' rights and interests are not violated (41, 56,

Table 6.1. Criteria to assess the acceptability of consent modifications for early pragmatic trials (EPTs).

Criteria	Definitions	Pre-market EPT (phase III)	Post-market EPT (phase IV)
Is the study minimal risk?	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 due to lack of market experience. Will require case by case judgment.
Is the study impracticable with regulatory consent?	*Cause*: Is the loss of data quality due to 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 due to extrinsic effects of regulatory consent.	Will require case by case judgment. It will be important to establish that the quality loss is due to extrinsic effects of regulatory consent.
	Effect: Is the expected loss of data quality so extreme that the trial is not worth doing?	Will require case by case judgment.	Will require case by case judgment.
	Alternative: Apart from modifying regulatory consent, are there no means or resources available that may be reasonably expected to counter the loss of data quality?	Maybe. Though majority of pre-market EPTs are industry-sponsored indicating some sort of availability of resources to enhance recruitment without compromising too much on real world conditions.	Maybe. Though most post-market 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 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) though 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, et cetera. Will thus require case by case judgment.
	Preference sensitive decisions		
	Other meaningful basis for decisions		
Overall assessment	Are all three conditions likely to be met?	No pre-market EPT will meet all three conditions.	Some post-market EPTs could to some extent meet all three conditions.
	Is a waiver of regulatory consent ever justified?	No pre-market EPT can be conducted with a waiver of consent.	No post-market EPT can be conducted with a full waiver of informed consent.
	Are alterations to regulatory consent ever justified?	No pre-market EPT can be conducted with alterations to regulatory consent.	Some post-market EPTs may be conducted with altered, simplified informed consent.

130). However, there is contention about the question whether bypassing informed consent for a randomized trial constitutes an infringement of patients' rights (130). For 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" (47) or, in a somewhat different wording, 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" (24).

The expectation criterion is necessary because in some studies, even in the absence of quantitative differences in risk of harm in the aggregate (136), patients may in fact have a meaningful basis for preferring one treatment over the other since there may be some qualitative difference between the two interventions being compared which may in fact make the choice a classic 'preference-sensitive' decision (35). Patients typically expect to have a say in such preference-sensitive decisions. In practice, many pragmatic trials will be interested in recording patient-centered outcomes which indicates that there are meaningful differences to be expected between compared treatments. In such cases, one can assume that patients would value having at least the option to actively choose one treatment (based on their own specific preferences) and declining random treatment allocation. The increasingly acknowledged shared decision-making model incorporates the value of patient preferences. For such research, full waivers of informed consent may compromise the valuable goals of shared decision-making, although altered yet still transparent consent procedures may not. Finally, even when there may not be a strong preference-sensitive choice at issue, the current empirical evidence shows that the general public has relatively high expectations regarding informed consent even for low risk pragmatic trials (138).

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 the different justifications for modifying regulatory consent requirements for pragmatic clinical trials in general and for making the differences between pre-market EPTs and post-markets EPTs apparent in comparison to pragmatic trials investigating standard of care treatments. Table 6.1 answers whether each condition in general terms is likely to be met by pre-market EPTs and post-market EPTs, and demonstrates how these features affect the permissibility of either waivers or alterations of regulatory informed consent.

Can some EPTs be minimal risk?

In assessing whether a trial involves minimal risk, a clear distinction exists between EPTs conducted in the pre-market phase and those conducted in the period directly following regulatory market approval. It seems unlikely that any pre-market EPT can be classified as

minimal risk. The experimental treatment is not an accepted treatment in terms of widespread use in practice or as 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, the presumption that pre-market EPTs pose greater than minimal risk is difficult to overturn. 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 (66, 125-127, 135).

For post-market 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 to 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, that is the common goal in the development of a new treatment) there will still be limited real world experience regarding its long term effects. This is markedly different for the comparison of two standard of care interventions that have been on the market for years. Thus, for post-market EPTs, there are considerations that need to be examined on a case by case basis.

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 regardless of whether 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 pharmaceutical company GSK in the United Kingdom—directed great efforts into inclusive enrollment of patients in a pre-market EPT. Though the actual publication of the study results does not mention specific challenges related to informed consent (26), a preliminary commentary published earlier by the investigators while the study was still ongoing does suggest 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 (25). The publicly sponsored post-market eLung and Retropro pragmatic trials also experienced substantial recruitment challenges, but faced much more difficulty in countering them (49). Physicians interviewed by the study team expressed that they perceived time to be the biggest barrier for patient recruitment, and that money could be used to 'create' more time (49). These examples show that there may be situations where the impracticability is something that can be overcome with sufficient resources to support regulatory consent procedures without fatally compromising the trial's real world nature. In such cases, one would need to question how much society (or a company) should be willing to

pay to obtain the answers to a specific pragmatic question. In cases where economic resources could not by itself eradicate recruitment problems due to regulatory consent procedures in a particular pragmatic trial, one would need to examine whether the social value of the trial could justify alterations to regulatory consent.

Such resource-dependent impracticability implies that a large pragmatic trial as representing the goals of a so-called 'learning health care system' (15) 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 for every pragmatic trial might lead to an overburdened and clogged up health care system. Commercial sponsors of one-off EPTs, on the other hand, would be incentivized to conduct such trials for business reasons (obtaining insurance coverage) and would also more likely have the financial means that could to some extent mitigate the practicability barrier. Of course, this does not rule out that some EPTs may be impracticable without some modifications to regulatory consent but such a determination would need to be made on a case by case basis. Our point is simply that for EPTs, the impracticability condition may be more difficult to meet, when compared to standard of care RCTs conducted in a learning health care system.

What kinds of patient expectations are relevant in EPTs?

In pre-market 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 be fully informed about a trial that tests experimental treatments.

In the early post-market phase, the treatments to be compared are no longer strictly experimental but accepted treatments in terms of regulatory approval. Nevertheless, when comparing post-market EPTs with pragmatic standard of care trials, more uncertainty exists with newly marketed interventions due to less experience and data. On the other hand, there might be data (for example, data used to obtain marketing approval) suggesting that the new intervention has a better risk-benefit profile than the current standard treatments. Thus, this could be framed as a classic 'preference sensitive' situation (the new treatment might be better but less is known about it); it can be expected that patients' preferences and expectations are highly relevant in such situations.

In post-market EPTs it then appears that 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. On the other hand, although new, the test intervention 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 post-market EPTs might be allowed to compare

interventions with the explanation of how the intervention will be chosen captured by a simpler consent process that mimics the course of everyday clinical practice (56).

IMPLICATIONS FOR INFORMED CONSENT IN EPTS

We have shown that that there are salient differences between pragmatic trials, especially between pre-market EPTs and pragmatic trials with standard of care treatments, in terms of risk and patient expectations. For pre-market EPTs, it is clear that from an ethical point of view modified consent for these trials will not meet the minimal risk condition nor the patient expectation condition; our analysis thus shows no pre-market EPT will qualify for a waiver of regulatory consent, and that any suggestion to alter regulatory consent before market approval should be regarded with extreme scrutiny (Table 6.1).

For post-market 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, the generally available resources (a brief modified consent process might allow pragmatic goals to be achieved with little extra resources) and patients' legitimate expectations to at least be informed that their (potentially new) treatment is being chosen randomly (e.g., in order to inform reimbursement decisions) rules against bypassing informed consent altogether. There is a possibility that some post-market 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, i.e., the compromise on data quality due to regulatory consent requirements is significant enough that the trial's value is threatened, even with significant resources. We note that we have put aside the question of what alterations to regulatory consent might exactly look like; for the purpose of this paper we have confined ourselves 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 earlier stages of the drug 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 a pragmatic trial evaluates, the harder it is to ethically argue for 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 to do so, and which thus erit 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 interventions could 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 comparative to existing standards. We analyzed how the oft-debated tension between requiring regulatory consent and enabling standard of care pragmatic trials affects our thinking about the acceptability of modifications (waivers or alterations) of regulatory consent for pre-market and post-market 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: (I) no pre-market EPT can be conducted with either a waiver or alteration of regulatory consent; (II) though no post-market EPT can be conducted with a waiver of regulatory consent, some might proceed ethically with an alteration to the regulatory procedure; and (III) thinking about EPTs can help to further pinpoint morally relevant issues of pragmatic trials across all the different stages of the drug life cycle.

CHAPTER 7

THE SOCIAL VALUE OF PRAGMATIC TRIALS

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ABSTRACT

Pragmatic trials aim to directly inform health care decision-making through the collection of so-called 'real world data' from observations of comparative treatment effects in clinical practice. In order to ensure the applicability and feasibility of a pragmatic trial, design features may be necessary that deviate from standard research ethics requirements. Examples are traditional requirements to seek written informed consent and to perform extensive data and safety monitoring. Proposals for deviations from standard research ethics practice have resulted in controversy about their ethical acceptability. One of the justifications for altered procedures is the allegedly high social value of pragmatic trials. In order to properly operationalize the concept in the ethical assessment of pragmatic trial designs, specification is warranted. We identified three determinants from common claims about a pragmatic trial's social value: (I) the extent to which the research question has real world relevance, (II) the trial design's ability to generate a real world answer and (III) the probability of direct uptake of the results by decision-makers in practice. Subsequently, we discuss how these determinants should be applied to the practice of pragmatic trials, and to what extent they might be applicable to explanatory trials.

INTRODUCTION

Randomized controlled trials (RCTs) that compare new or existing treatments with standards of care in routine health care settings are now commonly referred to as 'pragmatic trials' (10). Pragmatic trials deviate from more conventional RCTs as they aim to directly inform health care decision-making through the collection of so-called 'real world data' from observations of comparative treatment harms and benefits in clinical practice (141). The need to comply with certain trial regulations is believed to negatively affect the applicability and feasibility of pragmatic trials: any measure that deviates from 'real life' clinical conditions can potentially limit the validity and generalizability of the trial results (87), or render the trial practically impossible to conduct (e.g., in terms of economic resources or time spent) (44, 76). With regard to ethical requirements for research, some authors claim that pragmatic trials do not require full informed consent to be ethical, if the risks are minimal and patients' care is not meaningfully affected by the trial (47). Others dispute the ethical relevance of specific safety requirements for pragmatic trials (as, for example, demanded by the Good Clinical Practice guidelines), such as the need for enrolled physicians to comply with stringent study protocols to treat their patients (whereas in 'real life' this would not be the case) (49).

Alternative models for informed consent procedures have been proposed to resolve at least part of these challenges, yet in turn have given rise to controversy regarding the ethical acceptability of such alternatives (56). To what extent deviations from trial requirements are morally permissible will depend at least in part on whether a particular pragmatic trial fulfills sufficient justificatory conditions (130). One aspect of a pragmatic trial that seems to provide some moral weight to justifying such deviations is the expected social value of the research.

Since a pragmatic trial's expected social value might serve a justificatory purpose (i.e., potentially able to counterbalance alterations to informed consent procedures), it seems appropriate to substantiate what kind of claims pragmatic trials can make towards social value. Unless intuitive appeals to social value are made transparent, pragmatic trials run the risk of being categorically labeled 'socially valuable' simply because they are assumed to answer questions that aid clinical decision-making.

In this paper, we attempt to specify in what ways a pragmatic trial can express social value. Hereto, we will use the term social value to indicate 'the prospect of generating the knowledge and/or the means necessary to protect and promote people's health' (71). We envision that our specification of the social value of pragmatic trials will in some cases help to bolster the justification for alterations to current trial requirements, and in others, can make a stronger case for compliance to those same regulations in order to respect patients' rights. By making appeals to social value more material, this work has potential to contribute to better operationalization of the concept in the ethical assessment of pragmatic trial designs. Lastly, we discuss to what extent our framework for operationalizing social value in the context of pragmatic trials might prove useful to other types of research.

THE RISE OF PRAGMATIC TRIALS

Traditionally, regulatory authorities demand evidence from so-called 'explanatory trials' or 'efficacy trials' to inform market authorization decisions. These trials have the primary goal of obtaining scientific knowledge to understand the biological effects of drugs under 'idealized' or 'optimized' conditions (13). However, increasing concerns are expressed that explanatory trials may poorly predict the real world effectiveness of tested interventions (12). Once interventions are approved for the 'real world' (indicating different use and different end-users), treatment effects tend to change, not rarely for the worse. Lack of incentives to produce real world evidence on the comparative harms and benefits of new or widely used treatments has led to a knowledge void termed the 'efficacy-effectiveness gap' (4).

Pragmatic trials hold potential to bridge this evidence gap between efficacy and effectiveness by providing answers about the real world effectiveness of treatments comparative to existing treatment standards for the same indication (36, 45, 73, 74). Statisticians Daniel Schwarz and Joseph Lellouch coined the terms 'pragmatic' and 'explanatory' trials in their 1967 landmark paper (13). The distinction was drawn to make clinical investigators aware of the effects of their design choices: inability to match trial design to the research question inevitably leads to failure to provide reliable answers. Schwarz and Lellouch also argued that often pragmatic designs are more justifiable than explanatory designs, since the latter treat participants as a means rather than an end. In ethical decisions regarding whether to select more explanatory or more pragmatic design options, the authors concluded that all choices would have to "result in a certain degree of coherence" (13).

More than four decades after Schwarz and Lellouch's initial publication, Kevin Thorpe and colleagues found that many published trial designs or protocols were still not able to effectively answer the predefined research question (12). This finding prompted the development of the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) aimed at trialists to envisage what their trial design should look like in order for it to match the research question. Their work shows that all RCTs can be placed somewhere along a pragmatic-explanatory continuum and that as a consequence trial design protocols can and should be different—depending on the type of question—across nine domains (3). Consequently, a highly pragmatic trial would, among others, elicit (typically broad) eligibility criteria based on the characteristics of the population that would receive the treatment in clinical practice, recruitment and consent procedures that reflect routine care (e.g., verbal consent), minimal research protocol restrictions on physicians on how to prescribe treatments or follow-up patients, and no formal plans to improve compliance of the test treatment (19). In contrast, a very explanatory trial addresses the question of whether an intervention can work under idealized or equalized conditions, with the primary goal of acquiring mere scientific knowledge. Hereto, the population under study will need to be highly-selected using protocols that ensure the highest chance of treatment response (preferably including blinding and the use of a placebo control) (13).

It seems relevant to point out that the term 'pragmatic trial' has become somewhat of an umbrella term for a range of RCTs that display different design features and test a variety of

different interventions (35). Many understand pragmatic trials to predominantly cover RCTs evaluating the comparative effectiveness of standard of care interventions, though attempts have already been undertaken to design pragmatic trials comparing standards of care with novel treatments (26). We acknowledge these variations, but since our aim is to arrive at more general assertions about the social value of pragmatic trials we will set out from the most defining features of a pragmatic trial. A typical pragmatic research question then is: does treatment A, when compared to usual care treatment B, improve outcome C in patients with condition D once applied in routine clinical practice (the 'real world')?

CHALLENGES TO CURRENT ETHICAL OVERSIGHT

Promoting pragmatism in trials is of growing interest to a variety of stakeholders: patients and physicians require the best evidence to make treatment decisions, health policy-makers need to know which drugs are worth reimbursing (and which are not) and payers desire 'value for money' (2, 27). As promising as pragmatic trials may appear, they do come with a variety of challenges due to their intended real world nature. For example, the need to include large and heterogeneous patient samples creates all sorts of operational difficulties related to the management of multiple sites, while too much interference with routine practice compromises the real world nature of the trial (25). In terms of ethical challenges, it has been argued that trial regulations (such as the Good Clinical Practice guidelines (125)) contain requirements that disrupt clinical practice in ways that limit the validity and generalizability of the trial results (39, 43, 87), or that make some pragmatic trials impossible to conduct (76, 130). Some attest that certain pragmatic trials may still be ethical with less stringent requirements for informed consent procedures and/or oversight and safety measures (55).

Ruth Faden, Tom Beauchamp and Nancy Kass view pragmatic trials as fitting their notion of research efforts within a 'learning health care system', which is committed to continuous learning from clinical practice (15). It has been suggested that research activities within a learning health care system fall under a different ethics framework for research oversight (40, 41). The authors state that: "[C]urrent consent and oversight practices too often overprotect patients from research that has little effect on what matters to patients, whereas in other cases oversight practices underprotect patients from medical errors and inappropriate medical management because they make research to reduce these problems unduly burdensome to conduct" (47). For certain types of comparative effectiveness research, it might be ethically permissible to modify traditional requirements for clinical research in order to advance the goals of a learning health care system. The appropriate requirements for informed consent are probably the most debated. For a subset of trials investigating standard of care interventions, suggestions have been made to substitute the standard informed consent procedure with general notifications to inform patients about the possibility of ongoing trial enrollment in their care facility (so-called 'broadcast consent') (24). Scott Kim and Franklin Miller stress the importance of respect for the principle of respect for persons, and argue instead for a compressed, integrated consent model that preserves the freedom to opt out during a routine clinical encounter (56). Other

commentators have concentrated on the minimum selection of consent elements necessary to make informed decisions about study participation in pragmatic trials (61, 62).

Advocates of the learning health care system acknowledge that waiving certain investigator obligations as captured in traditional research ethics guidance warrants justification. Justificatory conditions pertain to the absence of more than minimal risk, the impracticability of the research otherwise and the assumption that patients would not reasonably object to enrollment with the deviation in place (47, 129, 130). Another aspect of pragmatic trials, which is almost always implied but has not received as extensive interpretation as these three necessary conditions, is the expected social value of the research. Since the concept appears to carry weight in counterbalancing deviations from conventional trial regulations that could infringe patients' rights at least to some extent, 'social value' needs to be given flesh and blood for it to be properly operationalized.

DETERMINANTS OF SOCIAL VALUE

In order to specify in what ways a pragmatic trial can have social value, identification of the appeals that have been made proves useful. Kirstin Borgerson juxtaposes the social value of pragmatic trials with that of explanatory trials when she states that: "Explanatory trials appear to investigate questions that are of indirect social value, since they do not intend to yield results that are immediately applicable in clinical practice. Pragmatic trials, by contrast, have direct social value, and so, are more likely to be immediately applicable to practice" (142). Borgerson argues that in cases where deviations from conventional trial design enhance social value, a pragmatic trial will usually be more justified than an explanatory trial. In the evaluation of the relative value of explanatory and pragmatic trials, Borgerson assigns greater value to trials in priority areas and those that are likely to generate greater improvements in health or well-being. These evaluations would favor pragmatic trials, according to Borgerson.

What can be construed from these claims is that a pragmatic trial has social value due to the fact that it generates *real world knowledge* that is *directly applicable* to *decision-making*. We discern three determinants that then affect this social value, knowingly, (I) the extent to which the research question has real world relevance, (II) the trial design's ability to generate a real world answer and (III) the probability of direct uptake of the results by decision-makers in practice.

Real world relevance of the research question

Pragmatic questions are formulated in such a way that their answers are informative to actions, which gives these questions some initial, inherent value. Nevertheless, pragmatic trials display a wide array of research questions, some of which are more valuable than others, in the sense that some research questions benefit society more than others. Such questions ought to be valued more because they address a societal need or hold potential to generate greater improvements to clinical practice. The typical pragmatic question 'does treatment A, when compared to usual care treatment B, improve outcome C in patients with condition D?' can be deconstructed to illustrate how the content of a pragmatic research question impacts a trial's social value.

First, element A could be assessed by its degree of 'therapeutic innovation', commonly understood to indicate the degree to which a new treatment entails additional benefits to patients when compared with existing treatment options. For novel pharmaceutical treatments, Motola and colleagues developed an algorithm to assess and display the level of therapeutic innovation based on the availability of previous treatments for the targeted condition and the therapeutic effect of the tested intervention (143). Such an algorithm could help to distinguish between interventions displaying either an important, moderate or modest degree of therapeutic innovation, to provide insight into the extent to which the needs of end-users are met by a new intervention (144).

Second, the relevance of the choice of comparator is signified by element B. In theory, pragmatic trials always compare the test intervention to the standard of care for the indicated condition. A standard of care comparison would, by definition, attribute a certain degree of social value to pragmatic trials. Yet certain comparisons have potential to yield greater improvements to clinical practice than others. Defining the appropriate standard of care to include in a pragmatic trial can be challenging (e.g., when there are different 'standards'). It sometimes occurs that the comparison group includes suboptimal usual care (86). Apart from concerns about risk of harm, such comparisons also raise serious issues with respect to the applicability of the results, and thus to their social value.

Third, social value can be increased through element C when it constitutes a clinically relevant endpoint or patient-centered outcome. The more clinically or patient-relevant a selected outcome is, the better the trial will be able to identify the more effective treatment strategy and to eliminate treatment options that do not optimally work for patients.

Finally, element D refers to patient populations with diseases or conditions for which a treatment either does not exist or is not sufficiently effective. In discussions about priority setting in drug research, these cases are referred to as 'pharmaceutical gaps' and are also present in diseases for which existing treatments will soon become ineffective (e.g., due to resistance) or when the delivery mechanism or formulation is not appropriate for the targeted patient population. Pragmatic trials that target such treatment gaps are socially more valuable than those pragmatic trials which, all other factors being equal, do not.

The design's ability to provide a real world answer

Though it may seem obvious, matching trial design to the predefined research question appears considerably challenging in clinical research. Schwarz and Lellouch observed that while trialists believed they were answering a pragmatic question, their results were in fact often explanatory by design. In order to be of any value to patients in practice, pragmatic trial results must be sufficiently generalizable to the real world. As mentioned before, Thorpe and colleagues have provided useful guidance on how to approach pragmatic questions to maximize generalizability. Assessing pragmatic trial designs by the degree to which their results will actually be generalizable to the real world is a useful means of envisioning their social value.

Some design elements that may be required in view of a pragmatic question, are arguably not considered appropriate means to acquire 'reliable, scientific knowledge'. Examples are the inclusion of placebo and other extraneous effects or allowing patients to switch treatment

groups while remaining in the study. However, if the question is indeed pragmatic and such design features actually capture what happens in routine clinical practice, the validity of the results will not necessarily be compromised. Maximizing validity and precision will always be requisite to ensure reliable, real world answers—no less in pragmatic trials than in explanatory trials.

Generalizability, validity and precision are key to information that can be reliably acted upon by health care decision-makers. Unfortunately, it often occurs that while on the drawing table pragmatic designs appear apt for providing reliable answers, in practice many of these trials encounter operational challenges that may negatively affect generalizability, validity and precision. A pragmatic trial's operational feasibility is therefore essential to consider in terms of social value assessments.

The probability of direct uptake of results

The greater the attempts of clinical investigators to increase the uptake of the trial results in practice, the more socially valuable the trial. One condition that may increase the applicability and uptake of the study results is a high probability of the study intervention becoming part of (reimbursed) real world health care. Another means of enhancing the uptake of the knowledge obtained, is through proactive and sustained engagement with the community from which patients will be recruited in all stages from study design to distribution of the study results (71).

Seemingly obvious but sometimes neglected, investigators conducting a pragmatic trial have the same obligations as all other trialists to make their trial protocols and results publicly available. If pragmatic trials are socially valuable due to immediate applicability of their results, a compelling argument can be made that pragmatic trialists have an even greater obligation to ensure direct access to the results through registration and publication, regardless of the outcome. The latter is relevant since pragmatic trials have a higher chance of the tested intervention not separating from the comparator due to cross-over and the use of active comparators. Though academic medical journals tend to have a dislike for indecisive results, it should be imperative that investigators commit to publishing such findings. Evidence that demonstrates lack of comparative effectiveness of novel treatments or equivalence of existing treatments is extremely useful for, in particular, health policy-makers.

IMPLICATIONS OF SOCIAL VALUE FOR PRAGMATIC TRIALS

Our goal was to substantiate in what ways a pragmatic trial can be socially valuable by clarifying appeals to the concept. We bridged resonating terms in discussions about the importance of pragmatic trials—such as 'real world relevance', 'immediate applicability' and 'informing health care decision-making'—with existing and new notions of what socially valuable research is. We came up with three determinants that can affect the degree to which a pragmatic trial has social value. The three determinants are not inherently unique to pragmatic trials but are nevertheless all necessary to ensure a pragmatic trial's idiosyncratic value.

As The Council for International Organizations of Medical Sciences (CIOMS) states in its recently updated guidelines, social value is a prerequisite for all studies involving human subjects

(71). There is a lower threshold, so to say, above which a trial or study has sufficient social value to justify the inclusion of human participants. This means all clinical studies will have to meet a social value requirement of some sort. For most clinical research—be it more pragmatic or more explanatory—it suffices to have some initial idea of the anticipated social value. However, since deviations from regulatory requirements might be necessary to achieve pragmatic goals, social value could provide a 'leverage' function, in addition to a 'threshold' function. In this particular operationalization of the concept, we do not view high social value as a pressing condition but rather perceive it to act as something that can provide some leeway for enabling a trial that would otherwise become less pragmatic. As such, a pragmatic question by itself could pass the initial threshold of social value, but modifying informed consent requirements to achieve ultimate pragmatism in the trial might not proceed ethically if the magnitude of the social value is limited.

One could argue that exactly because pragmatic trials are minimally disruptive to routine patient care, a justification in terms of social value for deviations from standard research ethics practice becomes less pressing. The assumption is that the risks patients face in many pragmatic trials are mostly offset by the potential benefits. So why is clarification important? Pragmatic trials make use of randomization to allocate treatments, which is evidently not a component of routine care. Some contend, however, that when there is genuine uncertainty about the relative risks and benefits of the compared treatments in practice, treatment allocation by physicians is just as random (55). For the random patient, even if the ex-ante estimates of relative risks and benefits of the compared treatments are different, there is no incremental welfare difference attributable to being in the trial as long as the allocation ratios in and outside the pragmatic trial are similar (136). For the specific individual, nevertheless, being in a pragmatic trial may affect his or her care in meaningful ways. Patients may have preferences regarding different types of risks related to different treatments. Kim and Miller conclude from this that it is crucially important to disclose the different types of risk patients may face due to being in a particular pragmatic trial (56). This argument shows that even though in the aggregate patients might not encounter any incremental difference in welfare by being either in or outside a pragmatic trial, randomization does mean that the trial can affect specific patients' personalized care. Whether bypassing informed consent constitutes an infringement of rights remains topic of discussion, but assuming it does and, for the sake of argument, that conventional trial regulations are apt to sufficiently protect these rights, the social value requirement as justification becomes apparent.

We do not intend to say that pragmatic trials are less justified because they require deviations from standard research ethics practice. Quite the contrary. But the reasons for choosing specific trial design features will always need to be argued for in compelling ways, be it idealizing elements or features that seem ethically contentious. Since pragmatic trials inevitably constitute research, clinical investigators will always have at least some obligations towards the patients enrolled. This is captured in standard research ethics guidance. How strong those obligations ought to be is then balanced by a number of factors: the type and nature of the risks involved, the impracticability of the research with a particular regulatory requirement in place and whether patients have legitimate expectations about having a say in the treatments they receive.

We cannot imagine that fulfilment of the first three conditions can offset the need for a social value requirement in order to allow for less stringent ethical and regulatory requirements in a pragmatic trial. As such, balancing of all these factors against proposed deviations requires specification of these factors in particular cases. To this end, we have attempted to flesh out what a 'socially valuable' pragmatic trial might actually mean. Since decision-making regarding the ethical acceptability of, for instance, alterations to informed consent requires the complex task of specification and balancing of all these factors, we will not attempt to demonstrate here how our conceptual clarification might actually help solve such practical issues. Thus, we highlight the need of more in-depth analysis on how to balance these factors.

We will present two idealized cases that illustrate how our specification might become relevant: two pragmatic trials submit a request for short verbal consent during a routine clinical visit since the trial would be impossible to conduct with full informed consent (let us assume due to selection bias). Both trials include minimal risk of harm to patients and it is assumed that both trials do not affect the patient-physician relationship in meaningful ways. The test arm in trial A consist of a newly approved drug for patients with a chronic illness for whom a variety of effective treatments are already widely available. The trial is designed to establish non-inferiority to a subset of usual care among a moderately selected patient population. Though the sponsor's motives for the trial are providing pharmacoeconomic evidence to gain insurance coverage, no discussions have taken place between the sponsor and a health technology assessment agency. Pragmatic trial B compares a newly approved drug with a high degree of therapeutic innovation compared to the only existing, moderately effective standard of care treatment for the targeted condition. High generalizability is ensured by recruiting patients from the population that would be using the drug in real life. Endpoints are chosen in cooperation with patients and physicians, and are endorsed by a health technology assessment agency as to affect coverage decisions. All other features are not meaningfully different between the two trials.

Comparing these cases by our determinants, trial B seems to better achieve the goal of directly improving real world clinical care and thus is socially more valuable than trial A. As such, verbal consent for trial A is more difficult to justify than for trial B. Whether trial A would still be feasible with a reduced consent form remains up for discussion. Though the examples represent exaggerated hypothetical cases, they do illustrate how lesser duties on researchers to comprehensively inform patients can only be reasonably argued for if patients can trust that deviations from conventional research ethics guidance in some way reflect the value of the research.

APPLICATION TO OTHER TYPES OF RESEARCH

Our framework specifically helps to ensure that deviations from conventional trial ethics procedures are backed up by a trial's social value in order to secure public trust and support for pragmatic trials. We follow Borgerson in her view that trial designs that enhance social value should be preferred, but we do not agree that mere direct applicability can be equated with social value—which would indicate that pragmatic trials by definition express higher social value

compared to explanatory trials. Instead, we point out that the social value among pragmatic trials is highly variable and that there are more aspects that determine their respective value. The determinants of our framework represent the degree to which real world needs are met and measure the translation of obtained knowledge into actions that extend beyond designing new studies. Though the determinants for pragmatic trials might capture part of a more explanatory trial's social value, we do not recommend completely relying on our framework to assess the value of explanatory trials. For example, any type of trial of which the results are not disseminated arguably has minimal social value; however, it does not seem right to disqualify explanatory trials on social value grounds because they do not directly relate to an actual clinical dilemma, or because decision-makers cannot use the results to change routine care immediately (145). Obviously, some explanatory research is necessary to advance health care in the longer run; in areas where there is much more uncertainty, controlled conditions may be the only way to unlocking mechanisms of action.

In a way, our framework supports thinking in terms of social value for all kinds of 'learning activities' in the real world: effectively, our framework values the presence of a relevant, real world question that provides a real world answer that is likely to be actively used by decision-makers to affect everyday practice. Though observational studies are subject to less stringent ethical and regulatory requirements—at least compared to RCTs—some deviations might still be desirable for practical reasons. In such cases, our social value assessment could similarly help determine whether there is some leeway for refraining from some of these regulatory requirements.

CONCLUSION

Pragmatic trial designs have given rise to controversy about the question whether it is ethically acceptable to deviate from traditional research ethics requirements for RCTs, such as written informed consent. One of the justifications offered for counterbalancing potential minimal rights infringements, is the trial's expected social value. Our concern is that an unspecified notion of social value limits operationalization of the concept in the ethical assessment of pragmatic trial designs. We thus identified three determinants of social value from claims that emerged in the debate: (I) the extent to which the research question has real world relevance, (II) the trial design's ability to generate a real world answer and (III) the probability of direct uptake of the results by decision-makers in practice. Further work is needed to assess how this understanding of social value relates to other factors considered important to the justification of pragmatic design features.

CHAPTER 8

GENERAL DISCUSSION: RESPONSIBLE USE OF PRAGMATISM IN RANDOMIZED TRIALS WITH NEW MEDICINES

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THE CASE FOR EARLY PRAGMATISM

Reliable "real world" data are important for our understanding of the relative benefits and risks of different pharmaceutical treatments once used by patients in routine clinical practice (44, 141). Today, many phase III randomized clinical trials are not designed in ways which inform clinical decision-making properly. The gap in knowledge between the efficacy of a drug in a clinical trial and its effectiveness once marketed in the real world of medicine results in numerous patients not receiving the best possible treatment. This also, at the same time, drives up health care expenditure (2, 38). Promoting the collection of real world evidence through pragmatic trials with new medicines, at the point at which they are approved for the market by a regulatory authority, is one way to improve the evidence-base for delivering patient care. In the long run this may also make the process of medicines development and evaluation more efficient and sustainable (8, 27).

However, to encourage trialists, research funders, oversight bodies and policy decision-makers to increase and accept pragmatism in randomized trials conducted around the time of regulatory market approval is challenging. At least one prominent hurdle for the design of pragmatic trials in general is the perceived tension between the pursuit of pragmatic goals and the need to comply with ethical and regulatory requirements for clinical trials (10, 37, 38). Ethical challenges have been identified with respect to informed consent procedures (47, 76, 129), risk determination (60, 134), the inclusion of vulnerable subjects (77), data monitoring (146) and the need for alternative ethical oversight (40, 41). Some preliminary work has already looked into the ethical and regulatory complexities of early pragmatic trials with new medicines. And yet this suggests that some pragmatic features become even more challenging the earlier they are introduced (78, 132).

Given the tension between ethical regulations and pragmatic goals, we suggest three ways that could help promote pragmatism in an ethically responsible manner. We specifically address 'early pragmatic trials', which we use to refer to randomized trials for evaluating new medicines either before, or directly following, their market approval. With a focus on the ethical opportunities in late phase III and early post-marketing research—where the difference between data on efficacy and effectiveness starts to take shape—we hope to responsibly guide the timely collection of real world data.

THE ETHICAL CONSEQUENCES OF HIGH-LEVEL PRAGMATISM

The PRECIS-2 wheel is a tool which has been developed recently to enable researchers conducting clinical trials to make best use of their avilable design options. It focuses on the applicability of a trial (the ability of trial results to be applied to the real world) by helping researchers to make the purpose of their trial explicit and to match their design choices to the intended purpose (3). However, some design choices may be deemed so pragmatic as to depart from what are generally considered appropriate measures for safeguarding the rights

and interests of trial participants. This means that potential conflicts might arise between the desire to address the needs of patients better, both in and outside trials, and the need to protect the rights and interests of patients as trial participants. We present some examples from across the nine domains of design choices covered by the PRECIS-2 tool, which illustrate how greater pragmatism might have ethical consequences (Table 8.1). What our table also shows is that, for some domains, opting for pragmatic design choices does not appear to conflict with conventional ideas about the protection of research participants in randomized trials.

EXPANDING PRAGMATISM AT LESS ETHICAL COST

Given the ethical difficulties of some pragmatic design choices, the opportunities for expanding pragmatism in less controversial domains should first be explored (Table 8.1). For example, using the PRECIS-2 tool, opting for pragmatic design choices to select and analyze outcomes does not at first appear to be ethically worrisome. It is therefore a relatively simple means of increasing the degree to which the results can be generally applied to patient populations in practice. Promising examples of this is the trend towards the collection of more patient-centered outcomes (20) and the increasing acceptance of Bayesian statistics (147). However, there is a potential for expanding pragmatism in an ethically responsible manner even in domains for which pragmatic choices might first appear problematic. With regard, for example, to the eligibility of participants, the age limit for participation could be increased, or patients with a comorbid condition could be included. At the same time, it would be best to steer clear of more controversial criteria for inclusion such as pregnant women, children or patients with cognitive disabilities (except where these groups make up a significant proportion of the target population).

TIMING MATTERS MORALLY

There are some salient differences between pragmatic trials which are carried out before market authorization, those conducted soon after it and those carried out well beyond (once the treatments have become so-called standards of care). These differences are relevant in determining whether a design choice is acceptable at each stage. Fine-tuning the timing of a pragmatic trial, based on weighing the advantages and disadvantages of a design feature at different stages may minimize potential ethical concerns.

Conducting a pragmatic trial prior to market authorization in a late stage of a phase III research offers an opportunity for decision-makers to be informed better and sooner about the realities, in practice, of the relative effectiveness of newly marketed medicines (8). These results can affect the decisions taken by regulatory bodies as well as reimbursement agencies, thereby improving patient access to effective and affordable pharmaceuticals. However, the lack of an independent authority having validated the safety and efficacy data in advance indicates that the drug chosen for the test intervention is still an experimental medication. Given the relative uncertainty of such a trial, and the fact that patients could reasonably expect that

Table 8.1. Potential ethical consequences of highly pragmatic design choices.

PRECIS-2 domain	Example of high pragmatism	Potential ethical consequences
Eligibility	Inclusion of children, pregnant women and elderly patients	Concerns about sufficiently protecting the rights and interests of vulnerable subjects
Recruitment	Short, verbal informed consent for a randomly allocated treatment	Concerns about sufficient degree of transparency and freedom of choice
Setting	Conducting the trial in a research-naïve setting	Concerns about the validity of the results
Organization	No additional training to increase the expertise of clinicians how to prescribe the test medication	Concerns about safe prescription of medication
Flexibility (delivery)	No measures in place to monitor the compliance of clinicians delivering the intervention	Concerns about optimal treatment of patients
Flexibility (adherence)	No measures in place to monitor patient adherence with the protocol	Concerns about optimal treatment of patients, and about the validity of the results
Follow-up	No follow-up contact with enrolled patients and outcome data collected by means of electronic health records	Concerns about optimal treatment of patients
Primary outcome	Selecting an outcome that is meaningful to patients, clinicians and policy-makers, such as reduction in hospital admissions	No apparent negative consequences
Primary analysis	Including data from trial sites or providers who do not meet recruitment targets	No apparent negative consequences

researchers apply measures similar to those required for more traditional phase III trials, certain pragmatic design features will be much more controversial, ethically, than those carried out at a later stage. For example, trying to achieve pragmatic goals by modifying regulatory informed consent procedures and striving, in general, for minimal interference with routine care, does not seem to be evidence of an adequate protection of patients' rights and interests.

The advantage of the early post-marketing phase of medicines evaluation is that clinical trials can be designed much more pragmatically since interventions are licensed to be used on the market. In a pragmatic trial with approved interventions, the borders between research activities and routine clinical care become blurred (40, 44). Nevertheless, by designing these trials after market authorization rather than before, there might be an unwanted delay between the approval and the reimbursement of the intervention (33). This inherently leads to a delay in patient access to the most effective, reimbursed health care since there is no substantial narrowing of the gap between efficacy and effectiveness. Moreover, at this stage, regulatory authorities can no longer take additional evidence into account in decisions concerning

marketing authorization. But, even so, these types of pragmatic trials provide the relevant information much sooner than those where pragmatism is used to assess the intervention once it has been labeled a standard of care intervention, which is, typically, after widespread use and years of clinical experience.

RECONCILING PRAGMATISM WITH ETHICAL CONCERNS

Some pragmatic trial design choices cannot be abandoned because of their importance to the applicability of the trial. In such cases, appeasing ethical concerns by expanding pragmatism in other, less controversial domains, may not be a viable solution. Nor will it help to postpone the trial until more certainty is reached about the benefits of the trial compared to its risks. One solution could be to let go of the intended goal of the trial, judging it not to be feasible if certain requirements have to be adhered to. However, several commentators have already made a case for requiring less stringent procedural measures for specific subsets of pragmatic trials to enhance their feasibility (24, 41, 55). There is some consensus that if the trial poses no more than minimal risk, the trial is infeasible otherwise, and if the trial procedures do not meaningfully deviate from what patients would have to undergo in the context of routine care, then informed consent might be obtained by simplified means. For example, by patients simply verbally agreeing to the trial (24, 66, 130). This is already reflected in recently updated EU regulations covering clinical trials (9).

Having said that, it becomes extremely hard to argue that unauthorized medicines pose no more than minimal risk. In this case it is unlikely that deviations from trial ethics regulations to enable pragmatic features in randomized trials with unauthorized medicines, would be sanctioned. This means that these pre-market trials will either need to rely fully on less controversial features to increase the level of pragmatism (such as recruiting from a more heterogeneous patient population) (26), or they should not be done at all at this stage. That is, if the research question cannot be properly addressed without the desired pragmatic feature. Once the interventions being tested in a pragmatic trial are accepted or approved by a regulatory authority, however, the matter changes. At this stage, some pragmatic trials could, potentially, meet the conditions for alternative trial procedures. If the compared interventions are used in accordance with their marketing license, the risks could be considered minimal. Then it is conceivable that a pragmatic trial may proceed ethically without, for example, the need for formal follow-up of patients, whose electronic health records are used for tracking outcome data (Table 8.1). However, even for early post-market pragmatic trials the infeasibility criterion needs to be maintained. A modification of the required procedure can be considered only if the applicability of the results cannot be ensured without the proposed pragmatic design feature in place.

Determining minimal risk and a trial's, often relative, infeasibility is evidently challenging. These conditions are, in theory, formulated as if they had clear cut-off values. However, the extent to which these conditions are met in practice is much harder to quantify. It seems more realistic to say that the underlying considerations will need to be balanced. To aid this

process, it is useful to draw attention to the types of interventions which might need a highly pragmatic evaluation directly following access to the market. This could be, for example, those trials for which it is evident that early pragmatism is beneficial or even imperative from a social point of view. This is because of their anticipated value to society. This may be a decisive factor when considering the effects, in practice, of the medicine to be tested. This may apply to several categories of interventions. The first category consists of trials or medicines which target types of illness where more traditional, explanatory, trials consistently fail to reflect the (typically more heterogeneous) nature of the patient population using the drug. In such cases, a pragmatic trial could make a significant difference to the observed outcome or safety. An example can be found in the area of cardiovascular disease, where, in practice, the typical patient has a number of comorbidities. The typical trial patient, however, does not. Another category is comprised of trials with medicines that target areas of diseases for which a variety of therapies, already marketed, exist, but which do not, sufficiently, accommodate the needs of individual users. For example, the needs of patients with mental disorders are usually quite patient-dependent. Even with a range of treatment options, some patients might not receive the treatments best tailored to their specific health needs. Accelerated, well-founded reimbursement based on sound real world evidence could then help to improve patients' disease management. A third category consists of trials or medicines in areas of high medical need, for which delayed or restricted access has a negative impact upon patients. A couple of examples here are delays in reimbursement or restricted label indications for medicines that are extremely costly, such as for orphan diseases or in oncology. The European Medicines Agency already recognizes this category as such in its programme of adaptive pathways (75).

WAYS FORWARD

Evidence obtained from randomized trials carried out in real world conditions, and at the time of market approval, is invaluable in order to accelerate patient access to the most effective and affordable medicines. Tension perceived between pragmatic goals and regulations applying to the ethics of drug trials discourages an early pragmatic approach from stakeholders. However, there are ways forward. Firstly, one could expand pragmatic approaches more generally. In particular one might focus on: outcomes of direct relevance to patients; on appropriate analytic methods; and, eligibility criteria that reflect the real world patient population. These are relatively accessible ways of increasing the practical relevance of randomized phase III trials and early post-marketing research. Secondly, adjusting the timing of the trial could provide a solution for obtaining timely real world answers in cases where a conflict arises between a pragmatic design feature and an ethical requirement. These measures, however, may not always be able to ensure, sufficiently, that results are applicable to practice. In this case, some pragmatic questions of evident social value could be addressed with less stringent requirements in the early post-market phase. The conditions here are that the risks are minimal, the research is infeasible otherwise and there is a sufficient degree of transparency and freedom of choice for patients.

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SUMMARY

Randomized controlled clinical trials (RCTs) are considered fundamental to the optimization of health care decision-making. That's why the drug development and evaluation process is dominated by so-called *explanatory* RCTs. Such RCTs are carried out in highly-controlled conditions to deliver the best evidence supporting market authorization of new pharmaceutical interventions. However, patients in explanatory phase III trials are very different from the actual patients who visit health care facilities in the context of "real world" clinical care. In the real world patients tend to be older, sicker and less keen on taking their medication. And what they care about is not necessarily bone density and systolic blood pressure, but rather whether the new drug keeps them out of the hospital. The focus on 'ideal' patients and situations means that for many patients it is uncertain whether a new drug on the market works better in real life than any of the other alternatives available. Explanatory RCTs are indispensable to the drug development process. That must be said. But the misalignment between efficacy data (can the drug work?) and effectiveness data (does the drug work in real life) suggests that explanatory RCTs cannot do all the work. The collection of so-called "real world data" has been proposed to complement the evidence-base for making health care decisions.

Pragmatic randomized trials are considered one of the strategies to obtain real world evidence. They contrast explanatory RCTs by question and design, since they aim to answer questions about the effectiveness of health interventions in routine care conditions. Recent calls have even gone out to design such trials already at the time of regulatory market approval of new interventions. Exploring ways to implement pragmatic trials in the process of drug development is a laudable goal in itself. Patients have an interest in receiving timely access to effective and affordable drugs, clinicians require a sound evidence-base for their patient prescriptions, health policy-makers need to know what drugs are worth reimbursing (and which are not) on a population level, payers want 'value for money' and regulatory authorities are willing to consider real world data as complimentary to market approval submissions (to estimate drug value in the long run). But departing from the classic paradigm of explanatory RCTs, especially as early as prior to market authorization, raises the question of ethical acceptability. Can we really just deviate from what research ethics has required ever since its first fundaments were laid in the 1940s? From a societal point of view, the only way to successfully and responsibly guide such innovative processes is to ethically evaluate the anticipated practice. This thesis therefore examines to what extent pragmatic trials with new interventions are ethically feasible.

This thesis starts out with an exploration of the ethical issues that have been related to pragmatic trials in general, along with those issues emerging in the context of practice-based comparative effectiveness research and real world evidence generation more broadly. The methodology used in **Chapter 2** is that of a systematic literature review. Qualitative assessment of the publications resulted in three main ethical questions connected to pragmatic trials: (1) what level of oversight should pragmatic trials require; (2) do randomized patients face additional risks; and (3) is a waiver of informed consent ethically defensible? This study lays bare a number of empirical assumptions someone might have about pragmatic trials. For example, that patients in trials

don't do worse than similar patients receiving the same treatments in the context of usual care. Or that randomization and systematic data collection aren't meaningful deviations from routine care. Despite the fact all reviewed publications dealt with post-launch pragmatic trials, these results were an important starting point for conceptualizing what challenges might arise in the pre-launch setting.

Chapter 3 presents a qualitative analysis that aimed to obtain insight into the actual experiences and perceptions of stakeholders in the field of drug research about the challenges of pragmatic trials or real world studies more generally. Semi-structured interviews were performed among a number of different stakeholders, including regulators, health technology assessors, industry partners, academics and patient representatives. Despite limited experience with pre-market pragmatic trials, stakeholders were willing to share their thoughts about a shift towards real world evidence collection at regulatory market approval. Ethically speaking, interviewees raised concerns about less controlled conditions creating safety concerns, comparison with usual care potentially compromising clinical equipoise, tailored or waivers of informed consent affecting patient autonomy and minimal interference with real world practice reducing the knowledge value of trial results. These concerns were thought to increase the earlier a pragmatic trial was planned. The four perceived challenges supported our findings from the literature review. Key ethical issues thus seemed to boil down to patient safety, clinical equipoise, informed consent and social value.

Since clinical investigators find lengthy informed consent procedures to be a significant operational barrier to the conduct of pragmatic trials, **Chapter 4** provides a comprehensive overview of the range of recruitment issues (including informed consent). Challenges of identifying, enrolling and retaining participants in a pragmatic trial were assembled from general literature searches and stakeholder interviews. This chapter gives recommendations about how to approach participant recruitment for a pragmatic trial. For example, to increase generalizability of the results all patients that are potential candidates for the treatments in routine clinical practice should be considered eligible for a pragmatic trial. Relevant subgroup heterogeneity (which means the drug might work better in some groups than in others) could be countered by increasing the relative proportion of the subgroup of patients, or by doing a separate trial with these groups. A more general problem of pragmatic trials is their low enrollment rates and expected high loss to follow-up. We describe a variety of practical strategies for keeping patients in a trial to ensure that the trial will be completed (so the results can actually be used in practice).

In **Chapter 5** we tackle the empirical assumption that informed consent procures can be detrimental to the quality of pragmatic trial results. A number of commentators have argued that the traditional consent model for RCTs poses substantial hurdles to the practicability of pragmatic trials: it would lead to recruitment difficulties, reduced generalizability of the results and selection bias (as we have seen in the previous chapter). Alternative consent models have been proposed to reconcile the goals of a pragmatic trial with a more 'tailored' consent procedure. In the first part of this chapter we assess the empirical assumptions about the infeasibility of some pragmatic trials due to traditional informed consent. In the second part we evaluate

the normative consequences of four alternative consent models that have been discussed extensively in the literature. We found that alternative consent models rely on different attitudes towards the principle of respect for persons and the related duty to inform patients. The models also represent different views on whether the common good entails particular patient duties to engage in clinical research. Especially consent waivers and broadcast notifications (about research participation being the default) imply strong duties on the side of patients and a high social value of the research. Our conclusion is that these normative consequences indicate that the empirical assumptions require considerable scrutiny, before the regulatory consent model can be adapted. To patients and the public, it is critical to convey the message that ethical standards cannot be modified simply to relieve investigators and sponsors from practical burdens (and related costs). It should be clear that if consent modifications are granted, that they are necessary for good reasons.

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With **Chapter 6** we take the first steps into the domain of 'early' pragmatic trials, so those trials conducted just before market authorization (late phase III research) or directly after (early phase IV research). Again, we use the example of regulatory informed consent procedures to assess the acceptability of ethically challenging pragmatic design choices in earlier stages of drug research. Specifically, we examine to what extent modifications (waivers or alterations) to regulatory consent would be ethical. First, we 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. We then apply those criteria to the pre-market and early post-market context. Our analysis shows that neither waivers nor alterations of regulatory consent will be ethically permissible for pre-market pragmatic trials. For post-market pragmatic trials with newly approved interventions, we conclude that waivers of consent will still be ethically problematic but that some studies might be ethically conducted with an alteration to regulatory consent.

In **Chapter 7** we explore how potential ethical concerns about pragmatic design choices might be reconciled. Many commentators have already written about the minimal risk criterion and about the principle of respect for persons. In this chapter we investigate the claim that pragmatic trials need to be done because of their direct value to society. We acknowledge that 'social value' can have a leverage function for permitting deviations from standard research ethics practice, but we remark that the concept is of little use without further specifying what it exactly *means*. We identify three determinants from common claims about a pragmatic trial's social value: (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. These determinants are meant to provide guidance on what a 'socially value' pragmatic trial might look like, so this aspect can actually be used in the ethical assessment of pragmatic design choices.

Early pragmatic trials can be of importance to drug development because they generate complementary data on the comparative effectiveness of new interventions as used in the real world. But perceived ethical and regulatory complexities seem to discourage early pragmatism.

Chapter 8 thus concludes with three ways to promote pragmatism in randomized trials in an ethically responsible manner. Firstly, we point to a few relatively accessible methods to increase the practical relevance of randomized phase III trials and early post-marketing research (such as the use of patient-centered outcomes). Secondly, adjusting the timing of the trial could provide a solution for obtaining timely real world answers in cases where a conflict arises between a pragmatic design feature and an ethical requirement (doing the trial shortly after market access instead of before). In cases for which these methods are insufficient, some pragmatic trials could potentially be conducted in the early post-market phase with less stringent requirements. Such trials would have to address questions of evident social value, under the condition that the risks are minimal, the research is infeasible otherwise and there is a sufficient degree of transparency and freedom of choice for patients.

NEDERLANDSE SAMENVATTING

Gerandomiseerde gecontroleerde klinische trials (*randomized controlled clinical trials*, RCT's) worden als fundamenteel beschouwd voor de optimalisering van de medische besluitvorming. Het proces van geneesmiddelenontwikkeling wordt daarom gedomineerd door zogeheten *verklarende* RCT's. Dergelijke RCT's worden in zeer gecontroleerde omstandigheden uitgevoerd om het beste bewijsmateriaal te leveren ter ondersteuning voor de markttoelating van nieuwe geneesmiddelen. Maar patiënten in verklarende fase III-trials kunnen nogal verschillen van de patiënten die gezondheidsinstellingen bezoeken in het kader van de alledaagse patiëntenzorg. In deze "echte wereld" zijn de patiënten doorgaans ouder, zieker en minder happig op het innemen van hun medicijnen. En wat deze patiënten belangrijk vinden is niet zozeer botdichtheid of systolische bloeddruk, maar of het nieuwe medicijn hen vervelende ziekenhuisopnames bespaart. De nadruk op 'ideale' patiënten en situaties betekent dat voor veel patiënten het onzeker is of een nieuw geneesmiddel op de markt beter werkt in de echte praktijk vergeleken met andere beschikbare alternatieven. Verklarende RCT's zijn onmisbaar voor de ontwikkeling van nieuwe geneesmiddelen. Dat moet zeker gezegd worden. Maar de matige overeenstemming tussen data over de werkzaamheid van een geneesmiddel (kan het medicijn werken in ideale omstandigheden?) en de gegevens over de (relatieve) effectiviteit ervan (werkt het geneesmiddel in de echte wereld?) suggereert dat verklarende RCT's niet al het werk kunnen verrichten. Daarom wordt door een aantal partijen voorgesteld om de kennisbasis voor besluitvorming in de gezondheidszorg aan te vullen met zogenaamde *real world data*.

Pragmatische gerandomiseerde studies worden beschouwd als een van de strategieën om *real world data* te verzamelen. Deze trials onderscheiden zich van verklarende RCT's door het type vraag dat ze stellen en het bijpassende studieontwerp. Zo richten pragmatische trials zich op de relatieve effectiviteit van medische interventies (zoals geneesmiddelen) zodra ze worden toegepast in de daadwerkelijke, klinische praktijk. Er wordt sinds kort zelfs opgeroepen om dergelijke trials al te ontwerpen rond het tijdstip van markttoelating. Het zoeken naar manieren om pragmatische trials eerder in het proces van geneesmiddelenontwikkeling te implementeren is een waardig doel op zich. Patiënten hebben belang bij het ontvangen van tijdige toegang tot effectieve en betaalbare geneesmiddelen, clinici vereisen een solide wetenschappelijke basis voor hun voorschrijfgedrag, beleidsmakers moeten op bevolkingsniveau weten welke geneesmiddelen het waard zijn om in het verzekerde basispakket op te nemen (en welke niet), verzekeraars willen 'waar voor hun geld' en regelgevende autoriteiten lijken steeds meer bereid om *real world data* in overweging te nemen voor keuzes omtrent markttoelating. Alleen het voorstel om voor pragmatische trials af te wijken van het klassieke paradigma van de verklarende RCT's roept de vraag op van ethische aanvaardbaarheid. Zeker wanneer er een plek voor pragmatische trials wordt voorzien voorafgaand aan markttoelating. Kunnen we eigenlijk wel zomaar afwijken van de fundamenten die de onderzoeksethiek heeft opgebouwd sinds de jaren 1940? De enige manier om dergelijke innovatieve strategieën succesvol en op maatschappelijk verantwoorde wijze te begeleiden is door de praktijk in *real-time* ethisch te evalueren. Dit proefschrift onderzoekt daarom in hoeverre pragmatische trials met nieuwe interventies ethisch haalbaar zijn.

Dit proefschrift begint met een verkenning van de ethische kwesties die in verband zijn gebracht met pragmatische trials, als ook die gerelateerd aan *real world studies* meer in het algemeen. De methodologie gebruikt in **hoofdstuk 2** is de systematische literatuurreview. De bevindingen van de studie laten de volgende drie centrale ethische vragen zien: (1) onder welke mate van toezicht moeten pragmatische trials komen te staan; (2) lopen gerandomiseerde patiënten extra risico's; en (3) kunnen pragmatische trials in aanmerking komen voor een vrijstelling (*waiver*) van het geïnformeerde toestemmingsvereiste? Deze studie legt hiermee een aantal empirische vooronderstellingen bloot die iemand zou kunnen hebben over pragmatische trials. Bijvoorbeeld, dat patiënten die aan trials meedoen het niet slechter doen dan vergelijkbare patiënten die dezelfde behandeling ondergaan in het kader van de routine klinische zorg. Of dat randomisatie en systematische dataverzameling geen betekenisvolle afwijkingen zijn van de reguliere patiëntenzorg. Ondanks het feit dat alle bestudeerde publicaties gingen over pragmatische trials met geregistreerde interventies, vormden de resultaten een belangrijk uitgangspunt voor de gedachtevorming over de uitdagingen die zich zou kunnen voordoen vóór markttoelating.

Hoofdstuk 3 presenteert een kwalitatieve analyse die tot doel heeft inzicht te verkrijgen in de feitelijke ervaringen en percepties van stakeholders ten aanzien van de uitdagingen van pragmatische trials en *real world studies* meer in het algemeen. We verrichtten semigestructureerde interviews onder diverse stakeholders, zoals toezichthouders, beleidsadviseurs, partners uit de industrie, academici en patiëntvertegenwoordigers. Ondanks de beperkte ervaring met pragmatische trials met nieuwe, ongeregistreerde interventies, waren stakeholders bereid om van gedachten te wisselen over de verschuiving van *real world data*-verzameling naar het tijdstip van markttoelating. Ethisch gezien uitten geïnterviewden hun bezorgdheid over potentieel bedreigde patiëntveiligheid in minder gecontroleerde omstandigheden, het bestaan van *clinical equipoise* wanneer een suboptimale controle-interventie wordt gekozen, aantasting van de autonomie van de patiënt door aanpassingen aan het traditionele toestemmingsvereiste, en over de verminderde kenniswaarde van de studieresultaten door minimale inmenging met de echte wereld. Deze bezorgdheid nam toe wanneer stakeholders reflecteerden op pragmatische trials met ongeregistreerde middelen. De vier vermeende uitdagingen kwamen overeen met onze bevindingen uit het literatuuronderzoek. Kernkwesties komen daarmee neer op patiëntveiligheid, *clinical equipoise*, het geïnformeerde toestemmingsvereiste en kenniswaarde voor de samenleving.

Omdat onderzoekers de tijdrovende procedures voor geïnformeerde toestemming als een aanzienlijke operationele belemmering zien voor pragmatische trials, geeft **hoofdstuk 4** een overzicht van het volledige scala van problemen bij de werving van deelnemers. Uitdagingen voor het identificeren, het includeren en het behouden van deelnemers in een pragmatische trial werden geïdentificeerd uit algemeen literatuuronderzoek en interviews met stakeholders. Dit hoofdstuk geeft aanbevelingen over hoe potentiele patiënt-deelnemers het beste benaderd kunnen worden voor een pragmatische trial. Bijvoorbeeld, de generaliseerbaarheid van de resultaten zou verhoogd kunnen worden door alle patiënten die potentiële kandidaten voor de behandeling zijn in de dagelijkse klinische praktijk in aanmerking te laten komen voor studiedeelname. En wanneer relevante heterogeniteit tussen subgroepen verwacht wordt (wat

betekent dat het geneesmiddel mogelijk beter werkt in sommige groepen dan in andere) zou het relatieve aandeel van de subgroep verhoogd kunnen worden, of zou men een aparte trial met deze subgroepen kunnen opzetten. Een meer algemeen probleem van pragmatische trials vormen de naar verwachting lage deelnemersaantallen en het verlies van deelnemers tijdens de follow-up. We beschrijven daarom een aantal praktische strategieën voor het behoud van patiënt-deelnemers in pragmatische trials, om zo de kans te verhogen dat de trial daadwerkelijk af wordt gemaakt (zodat de resultaten ook echt gebruikt kunnen worden in de praktijk).

In **hoofdstuk 5** gaan we verder in op de empirische vooronderstelling dat het klassieke proces voor geïnformeerde toestemming de waarde van een pragmatische trial afzwakt. Een aantal commentatoren heeft betoogd dat het klassieke toestemmingsmodel voor RCT's aanzienlijke obstakels opwerpt voor de uitvoerbaarheid van pragmatische trials: zo zou de procedure leiden tot onvoldoende deelnemers, verminderde generaliseerbaarheid van de resultaten en selectiebias (zoals we hebben gezien in het vorige hoofdstuk). Alternatieve modellen voor toestemming zijn voorgesteld om de doelstellingen van een pragmatische trial te verzoenen met een meer 'op maat' gemaakte toestemmingsprocedure. In het eerste deel van dit hoofdstuk evalueren we de empirische vooronderstellingen over de onuitvoerbaarheid van pragmatische trials als gevolg van het klassieke toestemmingsvereiste. In het tweede deel evalueren we de normatieve gevolgen van vier alternatieve toestemmingsmodellen die uitgebreid besproken zijn in de literatuur. We merken op dat elk alternatief toestemmingsmodel zich anders verhoudt tot het autonomiebeginsel en de daarmee verband houdende verplichting om patiënten te informeren over zorg en onderzoek. Ook vertegenwoordigt elk model verschillende opvattingen over de vraag of het algemeen belang een zekere (morele) verplichting van patiënten kan afdwingen tot deelname aan klinisch onderzoek. Vooral *waivers* van het toestemmingsvereiste en algemene meldingen over onderzoeksdeelname als de *default* impliceren aanzienlijke plichten van patiënten en een hoge maatschappelijke waarde van het onderzoek. Onze conclusie is dat deze normatieve gevolgen aanleiding geven tot een kritische evaluatie van de empirische vooronderstellingen, alvorens het klassieke toestemmingsmodel kan worden aangepast. Het is essentieel om naar patiënten en de samenleving de boodschap te communiceren dat ethische normen niet zomaar kunnen worden aangepast om onderzoekers en sponsoren van praktische lasten (en daaraan verbonden kosten) te verlichten. Het moet duidelijk zijn dat als deviaties van het klassieke toestemmingsvereiste worden gehonoreerd, dat die noodzakelijk zijn vanwege gegronde redenen.

Hoofdstuk 6 zet de eerste stappen in de richting van de 'vroege' pragmatische trials, dus die vlak voor markttoelating (late fase III-onderzoek) of direct erna (vroege fase IV-onderzoek). We gebruiken hier weer het voorbeeld van het klassieke toestemmingsmodel om de aanvaardbaarheid van pragmatische ontwerpkeuzes te beoordelen in eerdere fasen van het geneesmiddelenonderzoek. In het bijzonder onderzoeken we in hoeverre modificaties (*waivers* of wijzigingen) van het klassieke toestemmingsmodel gerechtvaardigd zijn. Hiertoe identificeren we eerst algemeen geaccepteerde, noodzakelijke voorwaarden voor dergelijke modificaties—namelijk, het onderzoek houdt minimale risico's in, het onderzoek is onuitvoerbaar met het klassieke toestemmingsvereiste, en het alternatief voor het klassieke model is niet strijdig

met de legitieme verwachtingen van patiënten. Vervolgens passen we deze criteria toe op de situaties voor en na markttoelating. Uit onze analyse blijkt dat *waivers* noch wijzigingen van het klassieke toestemmingsmodel toelaatbaar zijn voor pragmatische trials met ongeregistreerde middelen. Voor pragmatische trials met recent goedgekeurde interventies kunnen we concluderen dat *waivers* voor het toestemmingsvereiste nog altijd ethisch problematisch zijn, maar dat desondanks sommige studies wel verantwoord kunnen zijn met een wijziging van de klassieke vereisten.

In **hoofdstuk 7** onderzoeken we hoe ethische belangen mogelijk verenigd kunnen worden met pragmatische ontwerpkeuzes. Veel commentatoren hebben al geschreven over het criterium van minimaal risico en over het autonomiebeginsel. In dit hoofdstuk onderzoeken we de claim dat pragmatische trials hard nodig zijn vanwege hun directe waarde voor de samenleving. Wij erkennen dat de maatschappelijke waarde van een trial gewicht in de schaal kan leggen voor het toestaan van afwijkingen van conventionele ethische vereisten. Maar tegelijkertijd merken we op dat het concept weinig nut heeft zonder specificatie van wat het nu precies betekent. We onderscheiden drie determinanten—voortkomend uit gangbare claims—van de maatschappelijke waarde van een pragmatische trial: (1) de mate waarin de vraagstelling relevant is voor de "echte wereld" van de klinische praktijk, (2) het vermogen van de proefopzet om die vraag over de "echte wereld" ook daadwerkelijk te kunnen beantwoorden en (3) de kans dat de resultaten direct terechtkomen bij partijen die over de besluitvorming gaan. Deze determinanten zijn bedoeld om aanwijzingen te bieden over hoe een 'maatschappelijk relevante' pragmatische trial eruit zou kunnen zien. Daarmee kan het concept ook daadwerkelijk gebruikt worden in de ethische beoordeling van pragmatische ontwerpkeuzes.

Vroege pragmatische trials kunnen waardevol zijn voor het proces van geneesmiddelenontwikkeling omdat ze aanvullende gegevens leveren over de relatieve effectiviteit van nieuwe middelen in de echte klinische praktijk. Desondanks lijkt de ethische complexiteit de implementatie van vroege pragmatische trials te ontmoedigen. **Hoofdstuk 8** sluit daarom af met drie manieren om pragmatisme in gerandomiseerde studies te bevorderen, dat wil zeggen, op een ethisch verantwoorde manier. In de eerste plaats wijzen we op methoden die relatief toegankelijk zijn voor het verhogen van de praktische relevantie van gerandomiseerde fase III-trials en vroege fase IV-onderzoek (zoals het gebruik van zogeheten *patient-centered outcomes*). Ten tweede zou de timing van de trial aangepast kunnen worden in het geval er een conflict ontstaat tussen een pragmatische ontwerpkarakteristiek en een ethische vereiste (de trial vlak na markttoelating verrichten in plaats van ervoor). In gevallen waarin deze manieren geen uitkomst bieden, zouden sommige pragmatische trials mogelijk in fase IV uitgevoerd kunnen worden met minder strenge vereisten. Te denken valt aan trials die van evidente maatschappelijke waarde zijn, onder de voorwaarden dat de risico's gering zijn, het onderzoek onuitvoerbaar is anderszins en dat er voldoende transparantie en keuzevrijheid bestaat voor patiënten.

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Shona Kalkman was born on 1 February 1988 in Amsterdam, the Netherlands. In 2006 she graduated from the Vossius Gymnasium in Amsterdam with a Pre-University College degree from Leiden University, and started her studies in Medicine at Utrecht University. During her medical studies she completed several courses of the bachelor's program of Art History at the University of Amsterdam and gradually developed an interest in the medical humanities. She obtained her master's degree in Medicine in 2013 and continued working as a junior researcher at the Department of Clinical Pathology of the University Medical Center (UMC) Utrecht. In early 2014 she started working on this thesis as a PhD student at the Department of Medical Humanities at the Julius Center for Health Sciences and Primary Care of the UMC Utrecht. During her work at the Department of Medical Humanities, she spent three months as a visiting researcher at the Department of Bioethics of the National Institutes of Health in Bethesda (MD, USA). In 2016 she received a Master of Arts in Applied Ethics from Utrecht University. She currently works as an academic researcher at the Julius Center on a joint project with the department of Innovation Sciences of Utrecht University about responsible innovation in personalized medicine, funded by The Netherlands Organisation for Scientific Research (NWO). She teaches courses in medical humanities at the Faculty of Medicine and serves a position as ethics secretary of the Hospital Ethics Committee of the UMC Utrecht. She has written op-eds about scientific research for the online platform DeFusie.