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A Critical Examination of Informed Consent Approaches in Pragmatic Cluster-Randomized Trials

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Abstract

This thesis addresses the tension in pragmatic cluster-randomized trials between their social value and the requirement to respect the autonomy of research participants. Pragmatic trials are designed to evaluate the effectiveness of treatments in real-world settings to inform clinical decision-making and promote cost-efficient care. These trials are often embedded into clinical settings and ideally include all patients who would receive the treatments under investigation as a part of routine care. Trialists increasingly adopt cluster-randomized designs—in which intact groups, such as hospitals or clinics, are allocated randomly to study interventions—to simplify the inclusion of all patients. But including all-comers conflicts with the requirement to obtain written informed consent from research participants. Since informed consent is central to respecting patient autonomy, the question arises: how can the ends of autonomy and pragmatism be served simultaneously?

Some philosophers argue that patients have an obligation to participate in clinical research and that this may negate consent requirements. I argue that while there may be grounds for a *prima facie* obligation for patients to participate in clinical research, no compelling argument has demonstrated that the obligation is enforceable. Others assert that broad application of a waiver of consent will facilitate the conduct of pragmatic cluster-randomized trials. I demonstrate that this proposal sharply conflicts with the historical origins of the waiver. I articulate a novel moral foundation for the use of a waiver of consent and show that when trials evaluate treatments delivered directly to patients (e.g., drugs or vaccines), the autonomy interests at stake for participants are too substantial to permit its use.

My solution draws a distinction between consent requirements in existing policy and consent as an autonomous authorization. As many pragmatic cluster-randomized trials are conducted in primary care settings with no research staff, I argue that patient autonomy can be promoted and protected using clinical-style consent, in which health providers seek verbal informed consent from patients and document it in the electronic health record. This approach has been associated with high rates of recruitment and, thus, may satisfy both requirements for social value and respect for autonomy.

Keywords

Autonomy, informed consent, social value, moral duty, waiver of consent, pragmatic trials, cluster-randomized designs, philosophy, research ethics, bioethics

Summary for Lay Audience

Most clinical trials test whether a new medical treatment works in ideal conditions. But the real world is messy and unpredictable. Patients and doctors need to know whether medical treatments work when administered in doctors' offices and community hospitals. The solution: pragmatic trials. These trials mirror real-world clinical settings and include all patients who would receive the treatments under investigation as a part of their routine care. While patients are typically enrolled into a trial after they provide their written informed consent, soliciting their consent can disrupt the workflow of busy clinics to the extent that the trial no longer mirrors clinical practice. Seeking consent can also result in people refusing to participate, consequently undermining the aim of pragmatic trials to include everyone. Since consent is central to respecting the autonomy of prospective research participants, the question arises: when written informed consent is a barrier to the conduct of pragmatic trials, how can we respect patients' choices without undermining the aim to include all or most patients in these trials?

Some philosophers argue that patients have a moral duty to participate in pragmatic trials without consent, while others suggest that pragmatic trials will often meet the regulatory criteria to waive consent requirements. I argue that both solutions fail to respect patient autonomy. My solution is to return to the ethical foundation of informed consent. Informed consent is grounded in the principle of respect for autonomy, and it is meant to allow patients to autonomously authorize their participation in research. When written informed consent cannot be obtained in a pragmatic trial, I argue that alternative approaches to obtaining consent are appropriate. For example, health providers can seek verbal consent from patients and document their agreement in their medical records. This solution promotes patient autonomy while simultaneously facilitating the conduct of pragmatic trials.

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So many people walk around with a meaningless life. They seem half-asleep, even when they're busy doing things they think are important. This is because they're chasing the wrong things. The way you get meaning into your life is to devote yourself to loving others, devote yourself to your community around you, and devote yourself to creating something that gives you purpose and meaning.

—Tuesdays with Morrie, Mitch Albom

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Chapter 1: Introduction

Canada is a global leader in health research. Despite its many strengths in health care delivery and innovation, health care treatment decisions and policies often lack an evidence base. This results in the overuse of ineffective or harmful treatments, resulting in a substantial waste of health care expenditure and the underuse of effective treatment (Brownlee et al., 2017; OECD, 2017; WHO, 2020).[1] Ensuring treatments are safe and effective for patients and reducing health care expenditure requires pragmatic randomized controlled trials. Pragmatic trials are designed to evaluate the effectiveness of medical treatments in real-world settings to inform clinical decision-making and promote cost-efficient uptake of evidence-based practices (Schwartz & Lellouch, 1967; Zwarenstein & Treweek, 2009). These trials ideally include heterogenous groups of patients, occur in settings identical to clinical practice, require no additional staff or resources, and analyze data from electronic health records on patient-centred outcomes.

When designing a pragmatic trial, researchers can use standard patient-randomized designs in which individual research participants are randomly allocated to different study interventions. But researchers increasingly use novel cluster-randomized designs—in which intact groups, such as hospitals or clinics, are the units of randomization—to facilitate the conduct of pragmatic trials. Cluster randomization allows for most or all patients within a cluster to be treated with the same study intervention, resulting in the potential for greater external validity and lower costs when compared to standard patient-randomized trials. Thus, pragmatic cluster-randomized trials can efficiently generate robust evidence to inform the decisions of patients, health providers, and health system managers.

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[1] Recent evidence suggests that "one in ten patients in OECD countries is unnecessarily harmed at the point of care. More than 10% of hospital expenditure is spent on correcting preventable medical mistakes… [and] around one-fifth of health expenditure makes no or minimal contribution to good health outcomes" (OECD, 2017, p.3). In 2021, total health spending in Canada was approximately $308 billion, or 12.7% of Canada's gross domestic product (CIHI, 2022).

However, pragmatic cluster-randomized trials raise ethical issues that have not been adequately addressed. The foremost problem is the issue of informed consent. Pragmatic trials aim to mirror real-world clinical settings and ideally include all patients who will receive the treatments under investigation as a part of their routine clinical care. Soliciting patient's written informed consent can alter or disrupt the workflow of busy clinics to the extent that the trial no longer mirrors clinical practice and may result in people refusing to participate, consequently undermining the aim of pragmatic trials. Additionally, written informed consent can pose substantial methodological, logistical, and financial challenges to cluster-randomized trials. Hence, some researchers believe that informed consent is not appropriate for pragmatic cluster-randomized trials. But to conduct these trials without informed consent is clearly an infringement of patient autonomy. The question, then, is whether the infringement on patient autonomy is adequately justified by the social imperative to conduct this kind of research.

This thesis seeks to provide an answer to the question: how do we strike an appropriate balance between the requirement to respect patient autonomy and the imperative to conduct socially valuable pragmatic cluster-randomized trials? In this introductory chapter of the thesis, I provide the reader with background information on the complex issues at the intersection of ethics and clinical trial design. In section 1.1, I describe the philosophical problem of research ethics in its most general form to demonstrate the central role of autonomy and informed consent in the justification of clinical research involving humans. In section 1.2, I explain the central features of clinical trials—what is a randomized controlled trial, and what are the two main trial types (explanatory and pragmatic) and designs (patient-randomized and cluster-randomized)—to demonstrate the tension between informed consent requirements and the conduct of pragmatic cluster-randomized trials. In section 1.3, I further elucidate the tension through a real-world example of a pragmatic cluster-randomized trial conducted recently in the hemodialysis setting in Ontario, Canada. I conclude in section 1.4 with an outline of three sub-questions, to be addressed in the ensuing chapters of this thesis, that must be answered to provide a solution to the overarching question of this thesis.

1.1 The philosophical problem in clinical research

To conduct clinical research, researchers predominantly rely on people to volunteer as participants. But given that clinical research aims to determine the safety, efficacy, or effectiveness of health care interventions (i.e., treatments, procedures, policies, or practices), it is common—or, at the very least, possible—for people who participate in this kind of research to be exposed to a range of physical, psychological, social, or economic risks. Consequently, the philosophical question at the heart of research ethics is: when is it ethically permissible to expose people to risks in order to generate or contribute to knowledge for the benefit of others?

The first comprehensive attempt to answer this question appears in the *Belmont Report*, a statement of basic ethical principles that underlie the conduct of research involving humans with associated guidance to assure that these principles are followed (National Commission, 1978a). This document answers the question by appeal to three core ethical principles: beneficence, justice, and respect for persons. Each principle gives rise to ethical norms. When the norms for all three principles are fulfilled, exposing research participants to risks for the benefit of others is justified. Although these ethical principles are equally important, this thesis focuses on the conflict between beneficence and respect for persons; as such, further attention is only given to these two principles.

The ethical principle of beneficence requires that foreseeable harms are minimized, and that study participation poses a reasonable balance of benefits and harms in relation to the knowledge to be gained. According to Emanuel and colleagues (2000), "Only if society will gain knowledge… can exposing human subjects to risk in clinical research be justified" (p.2703). They state that clinical research must be socially valuable to be ethical—the knowledge gained, even without immediate practical ramifications, should lead to health care improvements. Due to limited resources, clinical research "that is likely to generate greater improvements in health or well-being given the condition being investigated, the state of scientific understanding, and the feasibility of implementing the intervention is of higher value" (ibid) and ought to be pursued.

Although the social value of any particular study may be difficult to quantify, international ethical guidelines state that socially valuable research is grounded in three factors: "the quality of the information to be produced, its relevance to significant health problems, and its contribution to the creation or evaluation of interventions, policies, or practices that promote individual or public health" (CIOMS, 2016, p.1). Research ethics committees are tasked with the review of proposed studies involving humans to ensure that studies conform to ethical guidelines. They have the authority to approve, reject, or stop studies, as their "main responsibility… is to protect potential participants in the research, [while taking] into account potential risks and benefits for the community in which the research will be carried out" (WHO, 2009, p.11). If a study has no prospect of social value—that is, there is no possibility of producing or contributing to scientific knowledge—then it would be unethical to allow the study to proceed. Thus, determining the degree to which a proposed study has social value is an important part of justifying the exposure of research participants to risks for the benefit of others.

The ethical principle of respect for persons dually requires "that individuals [are] treated as autonomous agents, and… that persons with diminished autonomy are entitled to protections" (National Commission, 1978a, p.4). While the concept of autonomy has been the focus of much controversy and debate, an autonomous person is generally understood as "an individual capable of deliberation about personal goals and of acting under the direction of such deliberation" (p.5). To demonstrate respect for autonomy (i.e., to fulfill the first requirement of respect for persons) means "to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others" (ibid). Conversely:

> To show a lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so (ibid).

The principle of respect for autonomy in clinical research dictates the ethical norm for researchers to obtain informed, voluntary, and revocable consent. Obtaining the

informed consent of a prospective research participant is an ongoing didactic process; it is not the discrete moment of a person's signature on a form. According to Canadian guidelines governing the conduct of health research involving humans, called the Tri-Council Policy Statement 2, informed consent "encompasses a process that begins with the initial contact (e.g., recruitment) and carries through to the end of participants' involvement in the project" (CIHR et al., 2018). In clinical research, recruitment often involves a determination of eligibility by one's health care provider and, if eligible, an invitation to participate in research. This is followed by a consultation with either their health care provider or a research coordinator who uses the consent form (often in paper format) as the basis to provide a full disclosure of all information necessary for making an informed decision.

Research regulations require a considerable amount of information about the research to be outlined in consent forms (CIHR et al., 2018).[2] As a result, many consent forms average 15 to 20 pages long and take approximately 60 minutes to read (Pandiya,

[2] "The information generally required [in consent forms] include: (a) information that the individual is being invited to participate in a research project; (b) a statement of the research purpose in plain language, the identity of the researcher, the identity of the funder or sponsor, the expected duration and nature of participation, a description of research procedures, and an explanation of the responsibilities of the participant; (c) a plain language description of all reasonably foreseeable risks and potential benefits, both to the participants and in general, that may arise from research participation; (d) an assurance that prospective participants: are under no obligation to participate and are free to withdraw at any time without prejudice to pre-existing entitlements; will be given, in a timely manner throughout the course of the research project, information that is relevant to their decision to continue or withdraw from participation; and will be given information on their right to request the withdrawal of data or human biological materials, including any limitations on the feasibility of that withdrawal; (e) information concerning the possibility of commercialization of research findings, and the presence of any real, potential or perceived conflicts of interest on the part of the researchers, their institutions or the research sponsors; (f) the measures to be undertaken for dissemination of research results and whether participants will be identified directly or indirectly; (g) the identity and contact information of a qualified designated representative who can explain scientific or scholarly aspects of the research to participants; (h) the identity and contact information of the appropriate individual(s) outside the research team whom participants may contact regarding possible ethical issues in the research; (i) an indication of what information will be collected about participants and for what purposes; an indication of who will have access to information collected about the identity of participants; a description of how confidentiality will be protected (Article 5.2); a description of the anticipated uses of data; and information indicating who may have a duty to disclose information collected, and to whom such disclosures could be made; (j) information about any payments, including incentives for participants, reimbursement for participation-related expenses and compensation for injury; (k) a statement to the effect that, by consenting, participants have not waived any rights to legal recourse in the event of research-related harm; and (l) in clinical trials, information on stopping rules and when researchers may remove participants from trial" (CIHR et al., 2018).

2010, p.98). The length of consent forms has also increased over time, and they are often criticized for their excessive length and complex wording (Albala et al., 2010, p.7). Consequently, prospective research participants must be given ample time to read and review the consent form and ask questions before signing it voluntarily. The purpose of the consent form is to document a patient's understanding and acceptance of the information within and to provide a reference for participants to revisit throughout the duration of the study. But the overall purpose of this written informed consent process involving consultation, discussion, and ongoing communication is to enable patients to autonomously authorize their participation in a particular research activity.

The reason informed consent is sought from prospective research participants, as described by Alexander Capron (2018), can be traced to three different yet overlapping sources: patients' right to self-determination, human rights law, and regulations. Capron argues that the first source of informed consent requirements in research can be found in a patient's right to self-determination. He states that "a physician who provides medical care with the best intentions may be horrified to be classed with a person who punches someone else in the nose, but each involves an unconsented touching and hence amounts to battery" (p.15). After reviewing a series of legal cases in which patient consent was not obtained for medical care, he concludes that "the consent requirement is fundamentally a manifestation of one's right to decide not just which harms to avoid but more simply which interferences with one's body… to permit" (ibid). Recognizing that consent to medical care began with a focus on patients' interest to be protected from *harm*, Capron maintains that consent to participate in research is about "protecting them against the *wrong* that occurs when they, as moral agents with the right and responsibility to chart their own lives and actions, are not given an opportunity to decide whether or not to accept an intervention involving their person or things intimately associated with their being" (p.16). In other words, patients have an unequivocal right to self-determination in both clinical practice and research.

The second source of informed consent in research, according to Capron (2018), is human rights law. Those familiar with research ethics often refer to the Doctors' Trial[3] and the subsequent development of the Nuremberg Code as the first moment in history where the requirement to respect patient autonomy appears in an international human rights document. The Nuremburg Code established a set of guiding principles that sought to distinguish legitimate and unlawful medical experimentation. Its first principle states:

> The voluntary consent of the human subject is absolutely essential. This means that the persons involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice… and should have sufficient knowledge and comprehension of the elements of subject matter involved as to enable him to make an understanding and enlightened decision (Nuremburg Code, 1947).

Similar language was adopted in the United Nations' (1976) *International Covenant on Civil and Political Rights* treaty, which states, "No one shall be subjected without his free consent to medical or scientific experimentation." Both human rights documents clearly articulate a strict requirement for informed consent in research.

Finally, Capron (2018) suggests that the third source of informed consent in research is federal regulations. This is in part because the Nuremburg Code was largely ignored by physician-researchers in North America and Europe. It was believed that the Nuremburg Code did not apply to non-Nazi research conducted by Americans and Europeans in laboratories, hospitals, and academic settings. Medical paternalism was the norm of the time, but this began to change with Henry Beecher's (1966) condemnation of twenty-two post-war unethical research projects in the United States, and the exposure of the unethical Tuskegee syphilis study in 1972 (Rothman, 1991). These events led to the National Research Act of 1974, the articulation of ethical principles for research in the *Belmont Report*, and the United States' new regulations governing the conduct of

[3] A series of tribunals in which many Nazi criminals were prosecuted for Holocaust war crimes, including their participation in the design and conduct of deadly medical experiments.

research in 1981. These regulations sought to replace medical paternalism with "shared decision-making, in which patients, closely advised by their physicians, control the ultimate choices about treatment and research" (Capron, 2018, p.23). These regulations would later become the Common Rule,[4] which established some of the first detailed requirements about the form and content of informed consent.

In sum, clinical research involves treating people as a means to the end of developing or contributing to generalizable knowledge that can be used to benefit others. To justify the conduct of clinical research, every study must have some prospect of generating social valuable knowledge, and the risks posed by participation must be minimized and reasonable in relation to the knowledge to be gained. Moreover, prospective participants must agree, through an informed consent process, to participate in research; using individuals without their consent is a violation of their autonomy. The fact that informed consent is grounded in patients' right to self-determination, human rights laws, and regulations means that any infringement on the requirement to respect the autonomy of research participants during the conduct of clinical research needs to be carefully considered and adequately justified.

1.2 The tension in pragmatic-cluster randomized trials

It should now be clear that there is a presumption in all research involving human participants that informed consent must be solicited and obtained from prospective research participants prior to their enrollment in a study.[5] But, as Lois Shepherd and Ruth Macklin (2019) note, "the bedrock requirement for obtaining informed consent from prospective research subjects… is eroding" (p.4). Indeed, an increasing number of proposals to conduct clinical research without informed consent have been appearing in the medical literature (Faden et al., 2013; Faden, Beauchamp & Kass, 2014). Capron

[4] Most recently revised in 2018, the Common Rule is the United States' regulations governing the conduct of research involving human beings.

[5] Recall that the principle of respect for persons dually requires that people are treated as autonomous, and "that persons with diminished autonomy are entitled to protections" (National Commission, 1978a, p.4). This second requirement means that, for some individuals who are not autonomous (e.g., young children), informed consent can and should be obtained from surrogate decision-makers (e.g., parents).

(2018) also fears that we are "moving away from informed, voluntary consent as the *sine qua non* for ethical research with human beings" (p.22). To understand the rising resistance to traditional research ethics norms, it is essential to understand the different ways in which clinical research can be conducted.

The randomized controlled trial is a rigorous methodology, often considered the gold standard, for generating high-quality scientific evidence. Randomization in its simplest form is any process that can assign participants to different study arms based solely on chance. For example, a coin toss can allocate a patient to either an experimental or control arm of a trial. When competently executed, randomization creates two or more study groups that are probabilistically similar on average with respect to known and unknown risk factors (Friedman et al., 2015, p.92). It also prevents the potential of bias in the allocation of participants to different study interventions (Shadish, Cook & Campbell, 2002, p.249).[6] Essentially, a study's internal validity—i.e., the extent to which a study establishes a causal relationship between a treatment and an outcome (p.53)—depends on randomization, and "most agree [randomization] is the best method for achieving comparability between study groups, and the most appropriate basis for statistical inference" (Friedman et al., 2015, p.123).

According to Daniel Schwartz and Joseph Lellouch (1967), randomized controlled trials are either "explanatory" or "pragmatic." An explanatory trial is "aimed at *understanding*. It seeks to discover whether a difference exists between two treatments which are specified by strict and usually simple definitions" (p.647, italics in original). In other words, it is designed to determine the efficacy of an intervention in laboratory-like or optimal conditions. To discover whether a treatment works in optimal conditions, trialists aim to recruit a homogenous group of research participants based on strict eligibility criteria. These trials often occur within specialized or academic centres,

[6] Often called selection bias, it occurs when researchers or patients influence the choice of intervention, either consciously or subconsciously. When selection bias is present, it can "easily invalidate the comparison" of study interventions (Friedman et al., 2015, p.92).

evaluate novel medical treatments or devices for regulatory purposes, and the results typically have downstream implications for patients.

Explanatory trials play an integral role in the development of new health care interventions. These trials are designed to test novel interventions in optimal conditions, often "to verify a biological hypothesis" or to prove a cause-and-effect relationship that may not otherwise be visible in normal conditions (Schwartz & Lellouch, 1967, p.644). If the experimental intervention is proved to be inefficacious in such favourable conditions, then researchers have essentially refuted a mechanistic hypothesis. In other words, the experimental intervention does not work. However, if the experimental intervention demonstrates signs of efficacy, the results of the explanatory trial cannot be generalized to justify using the new intervention in clinical practice. This is in part because the broader patient population is substantially and meaningfully different from those who participated in the explanatory trial.

While most randomized controlled trials have been explanatory, the last two decades has seen a growing interest in pragmatic trials and an almost exponential increase in their conduct (Zwarenstein & Treweek, 2009; Patsopoulos, 2011). A pragmatic trial is "aimed at *decision*. It seeks to answer the question—which of the two treatments should we prefer?" (Schwartz & Lellouch, 1967, p.647, italics in original). Essentially, they are designed to evaluate the effectiveness of an intervention in real-world settings and aim to generate evidence to support the decisions of patients, health care providers, and health system managers. Although randomized controlled trials are rarely purely pragmatic or purely explanatory, various design choices can make a trial more or less pragmatic (Loudon et al., 2013). Moreover, to determine whether a treatment is effective in real-world settings, pragmatic trials differ in important ways from explanatory trials. According to Taljaard and colleagues (2018),

> Trials that are more pragmatic have broader eligibility criteria, recruit participants at the time of presentation, include a diverse range of settings that mirror real-world circumstances, do not require highly specialized training or research personnel, give healthcare providers flexibility in how the intervention is

> delivered, require no special strategy for monitoring protocol compliance, follow and monitor patients as in routine clinical practice, have clinically meaningful and patient-centered outcomes, and include all randomized patients in analysis (p.2).

The reason for the increasing interest in pragmatic trials is, in part, due to the imperative to increase Canada's (and other countries') capacity to integrate high-quality scientific evidence into clinical practice. Kalkman and colleagues (2017) state that "a pragmatic trial has social value due to the fact that it generates *real world knowledge* that is *directly applicable* to *decision-making*" (p.140, italics in original). Pragmatic trials test a wide range of interventions (e.g., diagnostic, preventive, therapeutic, and delivery system interventions), and can test new interventions against current interventions used routinely in practice or test the comparative effectiveness of different interventions head-to-head (Taljaard et al., 2018). Consequently, the results of a pragmatic trial can tell us whether an intervention works and, more importantly, for whom it works in the messy circumstances of real-world settings.

When designing an explanatory or pragmatic trial, trialists can choose between two broad types of designs: patient-randomized designs and cluster-randomized designs. In a patient-randomized trial, individual patients are identified and recruited by researchers to participate in a study. Recruitment generally involves an independent assessment by a researcher to ensure patients meet specific eligibility criteria established in a study's research protocol. If eligible to participate, the written informed consent of the patient is solicited and either provided or refused. Once the written consent of a patient has been obtained, the patients (now research participants) are randomized to one or more experimental or control intervention arms and observed for their outcomes.

Cluster-randomized trials are different than patient-randomized designs in that the units of randomization are intact groups rather than patients themselves (Donner & Klar, 2000). These groups, called clusters, vary widely in type and size; for instance, clusters may be hospitals, medical practices, schools, communities, or geographical regions. In a cluster-randomized trial, clusters are identified by researchers and recruitment generally involves approaching a gatekeeper—who are "individuals or bodies who may be called

upon to protect the group-based interests that are affected by enrollment into a CRT [cluster-randomized trial]" (Weijer et al., 2012)—for permission to include their cluster in a trial. Once permission is granted, clusters are randomized to implement one or more experimental or control interventions within the cluster. Individual patients are observed for their outcomes.

Cluster-randomized trials are methodologically inferior and statistically more complex than patient-randomized trials (Taljaard et al., 2020). These trials require more research participants than patient-randomized trials because "outcomes from multiple patients in the same cluster are usually positively correlated" (p.254).[7] Cluster-randomized trials are also more prone to selection bias because individual patients are often identified and recruited after clusters have been randomized, and "unless this is done blinded to the cluster's allocation (which can be difficult or impossible to ensure), differential inclusion of patients may result" (ibid). For these reasons, the use of cluster randomization, as opposed to patient randomization, must be clearly justified.

According to the *Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials*, "reasons for adopting the CRT [cluster-randomized trial] design are diverse, and range from sheer necessity… to other scientific, practical, or logistical reasons" (Weijer et al., 2012). Cluster randomization is necessary when evaluating cluster-level intervention, which are interventions that can only be delivered to an entire cluster (Eldridge, Ashby & Feder, 2005, p.93). Examples of cluster-level interventions include water treatments delivered to groups of households with a shared water supply (Pickering et al., 2019), and community physical activity programs delivered to rural villages (Solomon et al., 2014). Cluster randomization may also be necessary when evaluating professional-level interventions, which are interventions directly delivered to health care providers that may have consequences for their patients. Examples of professional-level interventions include decision support algorithms delivered to physicians to assist with medication dosing (Nieuwlaat et al., 2014), and training sessions

[7] According to Taljaard and colleagues (2020), "the number of patients required for a [typical] CRT [cluster-randomized trial] is six times that under individual randomization" (p.254).

delivered to nursing home staff to implement evidence-based nonpharmacological interventions for managing aggressive patient behaviour (Rapp et al., 2013).

Sometimes cluster randomization is used to evaluate individual-level interventions, which are interventions directly delivered to patients such as prescribing physical activity regimens (Cheng et al., 2014) and providing patients with antibiotics (van Oostveen et al., 2018). In these cases, cluster randomization is not used out of necessity; in theory, patient randomization can be used. Given that cluster-randomized designs are methodologically complex and statistically inefficient, why do researchers opt to use a cluster-randomized design to evaluate individual-level interventions? In our review of a random sample of 40 cluster-randomized trials exclusively evaluating individual-level interventions, 25 trials (62.5%) reported a justification for the use of cluster randomization (Taljaard et al., 2020, p.259). The most common reported justifications were logistical or administrative convenience (15 trials, 60%), to avoid contamination[8] (13 trials, 52%), and to be more pragmatic or enhance external validity (5 trials, 20%) (ibid).

Indeed, cluster-randomized designs are thought to be inherently more pragmatic than patient-randomized designs (Ford & Norrie, 2016, p.459). This belief is exemplified by Eldridge and colleagues (2008), who state that "cluster randomised trials are pragmatic, measuring effectiveness rather than efficacy and should therefore be both internally and externally valid" (p.876). As stated above, internal validity refers to the extent to which differences identified between randomized groups are a result of the intervention being tested. Potential barriers to internal validity in cluster-randomized trials include insufficient sample sizes and a lack of blinding, but researchers can enhance internal validity by following guidelines and "recommendations for adequate power and

[8] Contamination occurs when the members of one group in a trial are exposed to the intervention that is meant for the other group. For example, "in a trial of dietary change, people in the control group might learn about the experimental diet and adopt it themselves" (Torgerson, 2001, p.355). Contamination can lead to a type II error, i.e., the "rejection of an effective intervention as ineffective because the observed effect size was neither statistically nor clinically significant" (ibid).

appropriate analyses" and ensuring that those who identify and recruit patients are blinded to their allocation status (p.878).

External validity, or generalizability, "refers to the extent to which study results can be applied to other individuals or settings" (Eldridge et al., 2008, p.877). Cluster randomization is believed to enhance the external validity of a randomized controlled trial. According to Dron and colleagues (2021), many patient-randomized trials "are carried out with specific types of patients under controlled conditions, with strict inclusion and exclusion criteria… for improved internal validity, but often this internal validity is achieved at the expense of external validity (explanatory trials). This type of trial design has been criticised for not reflecting real-world conditions and having unrealistic clinical populations, leading to poor external validity. As such, evidence from cluster trials is appealing to policy makers because their implementation can more accurately reflect the real-world roll-out of novel interventional strategies" (p.704). Additionally, cluster randomization allows for most or all patients within a cluster to be treated with the same study intervention. As a result, cluster-randomized trials require less research infrastructure to manage the allocation of study interventions. This facilitates a central aim of a pragmatic trial to require no additional staff or resources than would be available in clinical practice.

Concerns have been raised about whether cluster-randomized designs have greater external validity and lower costs than patient-randomized designs (Goldstein et al., 2018a; Taljaard et al., 2020). Because cluster-randomized trials require a greater number of participants than patient-randomized trials, cluster-randomized trials will generally be more expensive *if informed consent is required*. It is by obviating the need to recruit participants that makes these trials substantially less expensive. Moreover, cluster-randomized trials do not necessarily have greater external validity. According to Taljaard and colleagues (2020), "the perception that cluster randomization by itself increases the degree of pragmatism and external validity may rest on the misperception that the design facilitates inclusion of whole clusters *without the need for informed consent*" (p.255, italics in original). Thus, cluster-randomized trials are less expensive and have greater external validity when compared to patient-randomized trials only when informed

consent is not required. This creates a point of tension: high-quality evidence can be cost-efficiently produced in a pragmatic cluster-randomized trial only when informed consent from prospective research participants is not obtained.

Recent trends show that pragmatic cluster-randomized trials are increasingly conducted without informed consent. In our review of the reporting of informed consent in 1,988 pragmatic trials published between 2014 and 2019, we found that later trial start year, cluster randomization, self-identification as pragmatic, and higher income country settings were significantly associated with not obtaining consent (Zhang et al., 2021). Another review that examined the rationale, methodological quality, and reporting of cluster-randomized trials in critical care settings published between 2005 and 2019 found that "the need for consent was waived in most (31 [53%]) cRCTs [cluster-randomized trials]… [and] seven studies (12%) did not explicitly report their consent procedures" (Cook et al., 2021). We also conducted a review of cluster-randomized trials in the hemodialysis settings published between 2000 and 2019 and found that "three [cluster-randomized trials] (10%) received a waiver of consent… and five (16%) trials either did not discuss the consent process or it was unclear if patients provided informed consent" (Al-Jaishi et al., 2020a).

It is difficult to explain why there is a growing trend to conduct pragmatic cluster-randomized trials without informed consent. Yet, an increasing number of commentators argue that written informed consent conflicts with the aims of pragmatic trials and raises various challenges when using a cluster-randomized design. With respect to the aims of pragmatic trials, Jeremy Sugarman and Robert Califf claim that "obtaining conventional written informed consent may be not only ethically unnecessary but may render such research impracticable because of logistical burdens and may introduce selection bias" (2014, p.2381). The consent process may be costly, requiring additional research staff and resources, and it may also negatively impact recruitment and disrupt the workflow of busy clinics to the extent that the trial no longer mirrors clinical practice (Pletcher et al., 2014; Kim, 2018; Dal-Ré et al., 2019). This would invariably reduce the generalizability of the results and thereby undermine the pragmatic nature of the trial. With respect to cluster randomization, some argue that informed consent "is not relevant in a cluster

randomized trial because patients receive the same treatment regardless of whether or not they consent" (Vickers, 2014, p.619). Others refer to cluster randomization as a design that can help bypass or lessen the need for informed consent (Ford & Norrie, 2016; Ramsberg & Platt, 2018). Some go so far as to argue that if informed consent is required, "the efficiency gained by cluster randomization is lost" (Spence et al., 2018, p.816).

To conduct pragmatic cluster-randomized trials without informed consent is clearly an infringement of patient autonomy. But conducting socially valuable research that can inform clinical decision-making and promote cost-efficient uptake of evidence-based practices in clinical practice is integral to the advancement of health care. The question, then, is whether the infringement on patient autonomy is adequately justified by the imperative to conduct this kind of socially valuable research.

1.3 Illustrating the tension: the hemodialysis setting

A clear example of the imperative to conduct pragmatic cluster-randomized trials exists within nephrology. End-stage kidney disease is a leading cause of mortality and morbidity worldwide (Liyanage et al., 2015), and the global prevalence of kidney failure in 2017 was estimated to be 5.3 to 9.7 million people (Himmelfarb et al., 2020). Almost 23,000 Canadians are currently living with kidney failure (Liyanage et al., 2015), and over 5,000 Canadian patients start hemodialysis treatments every year (Forzley et al., 2017). Hemodialysis provides a life-sustaining treatment option for people with kidney failure. Although session duration and frequency can alter, hemodialysis often requires three- to five-hour treatments thrice weekly to clear toxins from the patient's blood and to remove excess fluid.

However, the quality of life of such patients is poor, life expectancy is short, and health care costs are high (Saran et al., 2018). According to Himmelfarb and colleagues (2020), "Mortality is very high among patients on dialysis, especially in the first 3 months following initiation of haemodialysis treatment. Approximately one-quarter of patients on haemodialysis die within a year of initiating therapy in HICs [high-income countries], and this proportion is even higher in LMICs [low- and middle-income

countries]" (p.575-576). In Canada, 58.5% of patients on hemodialysis die within five years (CIHI, 2020). This prognosis is worse than most cancers.

The leading cause of death in this patient population is cardiovascular disease, and death due to cardiovascular disease is 20 times higher for patients receiving hemodialysis than the general population (Cozzolino et al., 2018). This is because standard treatments used to effectively prevent cardiovascular disease in the general population (e.g., statins and anti-platelet drugs) are largely ineffective in patients on hemodialysis. Without the pace of treatment advancement seen in oncology, and as "the population of patients receiving dialysis continues to grow rapidly… [we can expect] millions of deaths resulting from kidney failure each year" (Himmelfarb et al., 2020, p.574). Thus, there is an imperative to develop new treatments for patients on hemodialysis to help reduce mortality and morbidity related to cardiovascular disease, and to enhance the quality of life of these patients worldwide.

Unfortunately, fewer clinical trials are conducted in nephrology than in other medical disciplines, and their quality is often poor (Trippoli et al., 2004). Many aspects of care for end-stage kidney disease are guided by clinical opinion and physiological studies, rather than from knowledge of treatment effects gained through rigorously conducted and sufficiently large clinical trials (Archdeacon et al., 2013; Levin et al., 2013). Embedding pragmatic cluster-randomized trials into the delivery of hemodialysis care has been proposed as an efficient method to generate practice-guiding evidence (Dember et al., 2016). Many facets of dialysis care, such as duration and frequency of treatments, electrolyte content of dialysate, and targets for blood pressure, could be informed by pragmatic trials.

One initiative to improve hemodialysis treatments for patients with cardiovascular disease in Canada was the Major Outcomes with Personalized Dialysate Temperature (MyTEMP) trial (Al-Jaishi et al., 2020b) (see Textbox 1). This pragmatic cluster-randomized trial examined the effects of temperature-reduced hemodialysis on cardiovascular mortality and major cardiovascular events over four years, from April 2017 to March 2021. Eighty-four dialysis facilities in Ontario, which delivered

hemodialysis treatments to over 15,500 patients, were randomized to provide either temperature-reduced personalized hemodialysis (0.5ºC to 0.9ºC below each patient's body temperature) or usual care (standard fixed temperature of 36.5ºC). Facilities were included in the trial if they had 15 or more patients and each facility's medical director agreed to adhere to their cluster's assigned treatment protocol. Over 98% of the data for patient baseline characteristics and outcomes were obtained from data sources housed at the Institute for Clinical Evaluative Sciences.[9] This allowed researchers to access anonymized health information about the patients in each hemodialysis facility for the purposes of analysis. In addition, each facility was requested to send de-identified data from 15 patients every month (a single page of data collection) to document whether the facilities were adhering to their assigned interventions.

Textbox 1: Details of the MyTEMP trial.

Aim: To test the effectiveness of outpatient hemodialysis centres randomized to either a personalized temperature-reduced dialysate or a standard-temperature dialysate protocol.

Design: Pragmatic, registry based, open-label, cluster-randomized trial.

Population: 84 hemodialysis centers in Ontario, Canada providing 4 million dialysis sessions to approximately 15,500 patients over a 4-year follow-up.

Interventions: Hemodialysis centers were randomized to provide dialysis treatments (1) between 0.5°C and 0.9°C below the patient's pre-dialysis body temperature, to a minimum dialysate temperature of 35.5°C, or (2) at the standard temperature of 36.5°C.

Data collection: 98% obtained through administrative data sources housed at the Institute for Clinical Evaluative Sciences. Other data, collected as part of routine care, was obtained from a random sample of 15 hemodialysis sessions per month.

Outcome: Composite of cardiovascular-related death or major cardiovascular-related hospitalization.

Ethics approval: Western University's Health Science Research Ethics Board, on behalf of 13 institutions overseeing 45 hemodialysis centres, approved the study with a waiver of consent. The remaining institutions received ethics approval and were granted a waiver of consent from their local research ethics committees.

[9] The Institute for Clinical Evaluative Sciences is an independent, non-profit corporation in Ontario, Canada that houses data collected through the routine administration of Ontario's health care system.

The MyTEMP ethics application was approved centrally by the Health Sciences Research Ethics Board at Western University through the streamlined review system managed by Clinical Trials Ontario.[10] This process allows a single qualified research ethics committee in Ontario to provide ethical review and oversight for multiple research sites participating in the same clinical trial. The research ethics approval was given on behalf of 13 institutions (overseeing 45 hemodialysis centres), and the remaining institutions received ethics approval from their local research ethics committees. Western University's research ethics committee approved the study and the researchers' request for a waiver of consent. This means that the trial proceeded without the prospective informed consent of any participant. The results of the trial have yet to be published.

The MyTEMP trial is not the only pragmatic cluster-randomized trial in hemodialysis proceeding without informed consent. Three other examples of hemodialysis trials with similar designs, recruitment procedures (i.e., no consent), and arguments for why informed consent is not required include the recently completed Time to Reduce Mortality in End-Stage Renal Disease (TiME) trial (Dember et al., 2019), the ongoing Randomised Evaluation of Sodium Dialysate Levels on Vascular Events (RESOLVE) trial (National Library of Medicine, 2016) and the proposed Outcomes of a Higher vs. Lower Hemodialysate Magnesium Concentration (Dial-Mag Canada) trial (National Library of Medicine, 2019).

The MyTEMP investigators argued that participation in their trial would pose no more than minimal risk to patients. In the event a patient receives treatment from a facility randomized to the usual care arm, which was approximately half of the patients in the trial, they would receive care that is no different from what they would otherwise receive outside of the trial. For those randomized to the novel intervention of lower dialysate temperature, known risks included the potential to feel cold as the blood returning to the patient is colder than body temperature. The researchers also argued that it would be methodologically, logistically, and financially impracticable without a waiver of consent. In effect, researchers believe that socially valuable research of this kind

[10] An independent, not-for-profit organization established with support from the Government of Ontario.

would be seriously impeded if informed consent from each prospective research participant was required. What underlies this dilemma is: how and to what degree ought we to respect the autonomy of patients given the imperative to conduct socially valuable pragmatic cluster-randomized trials?

1.4 Thesis question and outline

Once again, this thesis seeks to answer the question: how do we strike an appropriate balance between the requirement to respect patient autonomy and the imperative to conduct socially valuable pragmatic cluster-randomized trials? To provide an answer for this question, I will focus on the following sub-questions: (1) Do patients have an enforceable moral duty to participate in pragmatic cluster-randomized trials without their informed consent? (2) Can a waiver of consent be broadly used to facilitate the conduct of pragmatic cluster-randomized trials? (3) Can alternative models of consent promote and protect the autonomy of patients and facilitate the conduct of pragmatic cluster-randomized trials? Each of these questions represents a different approach to answering the overarching thesis question that requires careful consideration.

Those who take the first approach, described in chapter 2, aim to obviate informed consent requirements in pragmatic cluster-randomized trials through an appeal to a patient's moral duty to participate in clinical research. But do patients have a moral duty to participate in research? And, if so, does a patient's moral duty to participate in research override a researcher's duty to obtain informed consent? To resolve the tension in pragmatic cluster-randomized trials, proponents of this approach will argue that patients have an enforceable moral duty to participate in research. This is a duty that, by definition, acts as sufficient grounds to eliminate informed consent requirements in certain circumstances, thereby allowing socially valuable pragmatic cluster-randomized trials to proceed uninhibited.

Those who take the second approach, described in chapter 3, aim to obviate informed consent requirements in pragmatic cluster-randomized trials by arguing that a waiver of consent can be broadly used to facilitate the conduct of these trials. A waiver of consent can be granted by a research ethics committee if researchers prove that: "(1) the

research would not be feasible or practicable to carry out without the waiver or modification; (2) the research has important social value; and (3) the research poses no more than minimal risk to participants" (CIOMS, 2016, p.37). But where did these criteria come from? And when is it justifiable to conduct clinical research without informed consent? To resolve the tension in pragmatic cluster-randomized trials, proponents of this approach will posit various philosophical frameworks that can justify the conduct of pragmatic cluster-randomized trials with a waiver of consent.

I develop a third approach, described in chapter 4, to resolve the overarching question. Instead of exploring ways in which informed consent requirements can be eliminated, my approach is to explore whether alternative models of informed consent—namely, simple opt-out consent, integrated consent, short form consent, and electronic consent—can serve the ends of autonomy and pragmatism simultaneously. But are these consent models ethically permissible and practically feasible for pragmatic cluster-randomized trials? To resolve the tension in pragmatic cluster-randomized trials, I draw a distinction between consent requirements in existing policy and informed consent as an autonomous authorization and explore whether alternative models of consent can satisfy the conditions of an autonomous authorization.

It is only when we have answers to these three questions that we will have a firm grasp of when it may be permissible to trade-off patient autonomy against the imperative to conduct socially valuable pragmatic cluster-randomized trials. Though contextualized by the hemodialysis setting, this thesis seeks to offer broader guidance for informed consent issues in pragmatic cluster-randomized trials. Hence, in the concluding chapter of this dissertation, I address the generalizability of my arguments to other clinical contexts and conclude by raising questions for future research.

Chapter 2: The moral duty to participate in pragmatic cluster-randomized trials

Established in the previous chapter, I demonstrated that the requirement to respect the autonomy of research participants is in tension with the imperative to conduct pragmatic cluster-randomized trials. So how might we ethically proceed with the conduct of this socially valuable research? One approach to resolve this conflict, taken primarily by philosophers, has been to argue that patients have a moral duty to participate in clinical research that offers the prospect of direct therapeutic benefit. In brief, they argue against the view that people who participate in research are acting above and beyond the call of duty. They posit that, in certain circumstances, people ought to participate in activities that aim to contribute to generalizable knowledge and thereby improve the lives of future patients.

Although there has been considerable debate as to whether a moral duty to participate in clinical research exists, the arguments articulated in favour of a moral duty only support a *prima facie* duty; in other words, a duty to participate in clinical research that can be overridden by countervailing considerations. As I will demonstrate, these arguments, in and of themselves, fail to give an account of how socially valuable research can proceed without obtaining informed consent from prospective research participants. What is required to resolve the conflict is a convincing argument that supports an enforceable moral duty—a duty that, by definition, obviates the requirement to obtain informed consent. If such a moral duty exists, it would act as sufficient grounds to override the requirement to obtain the consent of prospective research participants, thereby allowing pragmatic cluster-randomized trials to proceed uninhibited.

Hence, in this chapter, I focus on the question: do patients have an enforceable moral duty to participate in socially valuable clinical research? In section 2.1, I provide an overview of the longstanding debate with regards to whether patients have a moral duty to participate in clinical research with direct therapeutic benefit. I demonstrate that their arguments only support a *prima facie* moral duty to participate in clinical research and argue that this cannot obviate a researcher's duty to obtain informed consent. Hence, in section 2.2, I construct three of the strongest arguments in favour of an enforceable

moral duty, and subsequently demonstrate that each argument succumbs to persuasive counterarguments. I thus conclude in section 2.3 that, barring any novel arguments, this approach fails to resolve the conflict between the requirement to respect patient autonomy and the imperative to conduct pragmatic cluster-randomized trials.

2.1 Overview of the debate

Hans Jonas (1969), in his canonical essay entitled *Philosophical Reflections on Experimenting with Human Subjects*, claimed that clinical research involving humans raised "inherently philosophical [questions] as it concerns… a genuine conflict of values involving principles of a high order" (p.220). The first principle—respect for autonomy—is fundamentally deontological: there is a widely held belief that we ought to respect the autonomy of individuals and not treat people instrumentally. The second principle is fundamentally consequentialist: social progress in medicine is for the greater good. According to Jonas, these principles conflict in clinical research since it often requires treating people instrumentally for the greater good. In other words, people are exposed to the risks of experimentation not for their own benefit, but primarily for the benefit of others.

Jonas (1969) claimed that our Western cultural tradition places a primary inviolability on the principle of respect for autonomy and the subsequent requirement to obtain informed consent. The primacy placed on respect for autonomy is justified, he argued, because "progress is an optional goal, not an unconditional commitment" and a "slower progress in the conquest of disease would not threaten society" (p.245). Jonas concluded that "society would indeed be threatened by the erosion of those moral values whose loss, possibly caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having" (ibid).

These philosophical reflections represent the predominant view in the research ethics literature: the primacy of respect for autonomy over social progress makes participation in clinical research supererogatory; it is praiseworthy but not morally obligatory. This means that participation in clinical research is akin to other supererogatory activities, such as donating blood or giving to charity. This view is

evidently reflected in international ethical guidelines. For instance, the Nuremburg Code (1947) states that the "voluntary consent of the human subject is absolutely essential," and the World Medical Association's Declaration of Helsinki (2013) states, "while the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects" (p.2191). Even contemporary international ethical guidelines for research involving humans state that "scientific and social value cannot legitimate subjecting study participants or host communities to mistreatment, or injustice" (CIOMS, 2016, p.1).

Recent empirical work conducted in the United States also substantiates the predominant view that participation in research is supererogatory (Weinfurt, Lin & Sugarman, 2019). In this study, a total of 2,994 English-speaking adults completed a national survey in which they answered questions measuring attitudes about their responsibility to participate in research. When prompted with the statement, "All patients have a responsibility to participate in some research studies to improve health care," 40.5% disagreed or strongly disagreed, while only 19.1% agreed or strongly agreed. When prompted with the statement, "I have a responsibility to participate in some research studies to improve health care," 31.5% disagreed or strongly disagreed, while 26.5% agreed or strongly agreed. Finally, when prompted with the statement, "No one has a responsibility to participate in research," 39.5% agreed or strongly agreed, while 22.9% disagreed or strongly disagreed. According to the authors, these findings suggest that "the majority of patients do not currently sense a responsibility to participate in research" (p.579).[11] Essentially, this study demonstrates the status quo. If someone argues that there is a moral duty to participate in research, they are challenging the status quo.

Nevertheless, there have been numerous attempts to argue that there is a moral duty to participate in clinical research involving direct therapeutic benefit. Proponents of these arguments claim that it is a *prima facie* moral duty. To say that a person has a

[11] It is worth noting that the authors of this study consider the terms "responsibility" and "obligation" as synonymous. According to the authors, "the initial draft of the survey used the term obligation, but respondents with lower literacy level found it to be confusing" (p.575).

prima facie moral duty to perform an action, according to William David Ross (1930), means that a person ought to perform that action unless it conflicts with another *prima facie* moral duty of equal or greater importance that favours not performing that action (or favours performing some other action instead). Ross gives the following example to show that one's *prima facie* duty of fidelity (i.e., to keep one's promises) can be overridden by the *prima facie* duties of beneficence or non-maleficence:

> If I have promised to meet a friend at a particular time for some trivial purpose, I should certainly think myself justified in breaking my engagement if by doing so I could prevent a serious accident or bring relief to the victims of one (p.18).

The original arguments in support of the *prima facie* duty to participate in clinical research were articulated (but not endorsed) by Arthur Caplan. Motivated by the fact that the research ethics literature at this time was focused on the protection of research participants, Caplan (1984) sought to explore "the moral reasons that ought to lead someone to participate in research in the first place" (p.1). He maintained that the reasons underlying a moral duty to participate in clinical research came in three forms: the moral duty is incurred because (1) we all accept and continue to accept the benefits of research, (2) participating in research produces goods and prevents harms, and (3) the knowledge gained from research is a public good. These three interrelated arguments are commonly referred to as the justice argument, the beneficence (or non-maleficence) argument, and the public goods argument, respectively.

Contemporary philosophers John Harris (2005), Rosamond Rhodes (2008), and G. Owen Schaefer (2009), among others, continue to promulgate these arguments (see Table 1). These authors argue against the predominant view in order to incite a cultural shift. Indeed, Schaefer and colleagues (2009) explicitly state that their argument does "not suggest that people have an obligation to become full-time guinea pigs. Instead, there needs to be a cultural shift in the moral framework that we bring to participation in research" (p.72). Rather than viewing research participation as supererogatory, the cultural shift would help to emphasize participation in clinical research as a moral good.

Table 1: Three arguments to support a *prima facie* duty to participate in clinical research.

Moral foundation	Reconstrued argument	Author endorsement
Justice	Premise 1: If we accept the benefits of research, then we must participate in the social practice which produces them; otherwise, we are free riding on others (i.e., acting unfairly). Premise 2: We all accept the benefits from the existence of the social practice of clinical research, and we will continue to accept the benefits from these and other advances. Conclusion: We have a duty to participate in clinical research.	Harris (2005); Rhodes (2008)
Beneficence/ Non-maleficence	Premise 1: If our actions can or will produce good or prevent something bad from occurring, then we have a duty to perform those actions. Premise 2: Participating in clinical research can or will produce good or prevent something bad from occurring. Conclusion: We have a duty to participate in clinical research.	Harris (2005); Rhodes (2008)
Public goods	Premise 1: Scientific knowledge produced by medical research is a public good. Premise 2: Participation in clinical research is a critical way to support this public good. Conclusion: We have a duty to participate in clinical research.	Schaefer et al. (2009)

But, in the words of Caplan (1984), "the arguments against a duty to serve as a subject in biomedical research seem to have been so persuasive as to have made the topic otiose" (p.3). Indeed, each of the arguments in favour of a *prima facie* duty to participate in clinical research have inspired many counterarguments (see Table 2). Although the three potential foundations and supporting arguments for the *prima facie* duty have been contested, the same arguments are being misappropriated to justify the conduct of research without informed consent. For example, a recent publication considers "how an obligation to participate should apply to consent waivers in the context of data research"

(Ballantyne & Schaefer, 2018, p.392). The authors argue that a *prima facie* duty "can ground waivers of informed consent for secondary research using public sector health data, even when obtaining such consent would be practicable" (ibid).

Table 2: Eight arguments against a *prima facie* duty to participate in clinical research.

Moral foundation	**Criticisms**
Justice	It is unclear that those who participated in research in the past were creating a debt that had to be discharged by those who reaped the benefits of their participation; if so, this undermines any altruism of their choice to participate (see Caplan, 1984). Merely benefiting from those who have previous participated in research is not morally objectionable. For example, we all benefit from the risks and burdens assumed by firefighters, but no one supposes that everyone has a duty to be a firefighter (see Schaefer et al., 2009). The argument assumes we all benefit from research, when millions of people worldwide have little or no access to its benefits (see de Melo-Martin, 2008).
Beneficence/ Non-maleficence	Proponents do not explain why one has a specific obligation to participate, rather than a *prima facie* duty to promote the welfare of others or to contribute to research through other beneficent acts such as donating to the research enterprise (see Shapshay & Pimple, 2007; Schaefer et al., 2009) Empirical research indicates that participating in research rarely produces good or prevents harm since the failure rate of clinical research is high and a lot of research is wasteful and lacks value (see Yarborough, 2017).
Public goods	It is not evident that health, safety, or scientific knowledge are public goods (see Jonas, 1969; Fried, 1974; Caplan, 1984). While an individual might be obligated to engage in activities to maintain public goods, it is unclear why such an obligation would extend to the improvement or advancement of public goods (see Jonas, 1969; Caplan, 1984). Most people already contribute to research without active participation, e.g., people contribute to public goods by paying for health care through taxation, insurance premiums, or out of pocket (see Allhoff, 2005; Brassington, 2008)

But a *prima facie* duty to participate in clinical research, in and of itself, cannot obviate a researcher's duty to obtain informed consent. According to Rhodes (2017), the fact that "we have a duty to participate in biomedical research [means] that it is something that each of us should do, that it is our obligation to participate, that

participation is the right thing to do, and that failing to participate, without significant justification, is wrong" with the caveat, "nothing that I say involves forcing people to become participants in clinical research" (p.319). This is because an individual may have conflicting *prima facie* duties such that the duty to participate in clinical research does not prevail.

The demands of the *prima facie* duty, then, is that people should say "yes" when asked to participate; if they say no, without reason, they are acting immorally. While those engaged in the debate rarely clarify what counts as a sufficient reason not to participate in clinical research, Sandra Shapshay and Kenneth Pimple (2007) claim that "when participation requires nothing more than a minor inconvenience, you should. […] Insofar as the demand of participating is greater, in terms of time, hardship or risk, a person is justified in spending his or her time, money and effort in discharging her [*prima facie*] obligations in another way" (p.417).

Whether a *prima facie* duty to participate in clinical research exists is therefore inconsequential to the question of how we can proceed with pragmatic cluster-randomized trials without the informed consent of prospective research participants. What is required to resolve the issue is a persuasive argument supporting an enforceable moral duty. An enforceable duty, by definition, is one that cannot be overridden by countervailing considerations. In the context of clinical research, an enforceable duty means that people can justifiably be conscripted into certain studies without their informed consent, thereby allowing pragmatic cluster-randomized trials to proceed uninhibited by the requirement to solicit and obtain consent. Thus, only when there is an enforceable duty can we set aside informed consent requirements.

This point is worth repeating: why argue for an enforceable moral duty to participate in clinical research, and how might this change the status quo? According to Angela Ballantyne and G. Owen Schaefer (2018), an enforceable duty means that "researchers would no longer be required to demonstrate that gaining consent is impracticable" (p.393) to be granted a waiver of consent from a research ethics

committee.[12] In fact, if an enforceable moral duty exists, they state that "it could be ethically acceptable for researchers not to seek consent from them even if obtaining consent were practicable" (p.394).

2.2 An enforceable duty to participate in clinical research

The literature on an enforceable moral duty to participate in clinical research is sparse. Only two substantive arguments have previously been articulated. The first argument, posited by both Harris (2005) and Rhodes (2005; 2017), is grounded in social contract theory. In section 2.2.1, I explicate this argument that suggests our moral duty to participate in clinical research is analogous to our civic duty to participate in the judicial system. However, I provide two counterarguments: I argue that the analogy between these two systems is weak, and that the implication of their argument is either an unjust or practically unworkable research system.

In section 2.2.2, I explicate and strengthen another one of Rhodes' (2008) arguments. This argument, grounded in Kantian deontological theory, suggests that participation in clinical research is mandatory when it aims to preserve one's own life or autonomy because participating in this kind of research is an act that offers the best chance for rational agents to fulfill their perfect duty of self-preservation. But I argue that, given the nature of clinical research, it cannot be guaranteed that participation offers any chance for achieving the ends of self-preservation. I also demonstrate that a perfect duty to participate in clinical research is inconsistent with Kant's categorical imperative.

It is rather surprising that no attempt has been made to construct an argument in support of an enforceable moral duty to participate in clinical research grounded in consequentialist theory. It may be that consequentialists generally find it difficult to

[12] Recall from the introductory chapter of this thesis, a waiver of consent can be granted by a research ethics committee if researchers demonstrate that: "(1) the research would not be feasible or practicable to carry out without the waiver or modification; (2) the research has important social value; and (3) the research poses no more than minimal risk to participants" (CIOMS, 2016, p.37).

generate any obligations with binding force.[13] Nonetheless, in section 2.2.3, I construct a robust argument grounded in consequentialist theory. This argument, following Peter Singer's argument for a moral duty to donate to charity, posits that if patients have the power to prevent suffering and death from occurring without sacrificing anything of comparable moral importance by participating in clinical research, then they have an enforceable moral duty to do so. However, I argue that the consequential argument, while potentially true for acts of donation, rests on a false empirical assumption in the context of clinical research, and that the implication of this argument is a research system that allows for patients to be limitlessly exposed to serious harms, including risk of death, without their informed consent.

2.2.1 The social contract argument

The first argument invoked to support an enforceable moral duty to participate in clinical research stems from Hobbesian and Lockean moral and political philosophy, in which they generate duties by appeal to a tacit cross-generational social contract (see Lloyd & Sreedhar, 2018; Tuckness, 2020). Briefly, this view maintains that people are free and equal in the state of nature, a state without government or duties to each other. But since this is a state of perpetual conflict (as self-interested people compete for limited resources and power), each individual person concedes their independence by agreeing via a social contract to obey a sovereign power that has the authority to create and enforce laws. Accordingly, the social contract to obey the sovereign creates certain duties; for instance, the duty to obey the laws established by the government, the duty to participate on juries to aid in the administration of justice, and the duty to pay taxes to support the common defense.

The central principle is that people form societies with governments that provide, among other things, justice and defense for its citizens. The citizens, by agreeing to live in these societies, incur duties to their community. One problem with this account is that

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[13] Since the consequentialists' foundational principle is to always act to maximize utility, the good, or the happiness of the greatest number, then moral duties seemingly have no binding force. For example, a duty to repay creditors can be overridden if a person can maximize the good for more people by donating all their money to charity.

few people have explicitly agreed to establish a government to which they incur these obligations. Locke's solution is to rely on a tacit agreement: by living in a society or by accepting the benefits provided to you by living in a society, you have tacitly agreed to the social contract and therefore incur certain duties (Tuckness, 2020).

Contemporary philosophers pick up on the tacit cross-generational social contract to argue that an enforceable duty to participate in clinical research is generated alongside the other duties generated under social contact theory. They provide arguments by analogy, citing participation on a jury and paying taxes as duties to our community that override individuals' autonomy. For example, Harris (2005) states that there are "a wide variety of what we might term 'mandatory contribution to public goods.' […] Taxation is of course the clearest and commonest example" (p.244). He continues with another example:

> There are many senses in which participation in vaccine or drug trials involve features relevantly analogous to jury service. Both involve inconvenience and the giving up certain amounts of time. Both are important public goods. [Both are] an integral part of 'due process,' helping to safeguard the liberty and rights of citizens (ibid).

He concludes, "we do not usually insist on informed consent in such cases [of moral and civic obligations], we are usually content that they merely consent or simply acquiesce" (p.245).

Another argument by analogy comes from Rhodes (2005), who provides the following example:

> In the same way that we have endorsed laws that require us to pay taxes and to serve on juries, reasonable people should accept an obligation to periodic service as research subjects… To withhold endorsement from such a policy would be taking advantage of the kindness of others—that is, being a free-rider on the system and failing to recognize the moral equality of others—hence, unreasonable. In the sense that no reasonable person could withhold agreement

> without injustice, we should subscribe to a social contract for reasonable research participation when others are willing to commit themselves as well (p.25).

Their argument is essentially this: by tacitly agreeing to live in a society whose government provides publicly accessible health care—regardless of whether one accepts that care—citizens incur a duty to participate in clinical research. Since enforceability is justifiable in the case of jury duty and taxation, "the same or indeed more powerful arguments would surely justify it in the case of science research" (Harris, 2005, p.244-245).

But Harris and Rhodes refuse to accept the consequences of their own arguments. Harris (2005) claims that "[his] own view is that voluntary means are always best and that any form of compulsion should be a last resort to be used only when consensual means had failed or where the need for a particular research activity was urgent and of overwhelming importance" (p.245). Rhodes (2005) states that, "informed consent would certainly have an important role within [her] framework" (p.26). This suggests that, for most clinical research, Harris and Rhodes believe that the requirement for informed consent should remain. Indeed, Harris (2005) explicitly states, "I am not here advocating mandatory participation in research, merely arguing that it is in principle justifiable, and may *in certain circumstances become justified*" (p.245, italics added).

What, then, are the circumstances in which there is a justifiable enforceable duty to participate in clinical research that obviates the requirement to obtain informed consent from prospective participants? According to Harris (2005), it is reasonable to assume that informed consent is not needed when: (1) the research aims to provide "significant benefits to humankind;" (2) "the costs and risks involved [to the participant] are minimal;" and (3) the research "is in their own and the public interest" (p.245). According to Rhodes (2017), "when the physical risks or burdens involved are insignificant and the study is scientifically important, informed consent may also be unnecessary" (p.325). Note that, as Ballantyne and Schaefer (2018) observed, these criteria are the regulatory criteria to obtain a waiver of consent without the criterion that obtaining informed consent would render the conduct of research impracticable.

Pragmatic cluster-randomized trials in the hemodialysis setting provide a compelling case in which an enforceable duty would be justified on their account. Consider the MyTEMP trial (see Textbox 1). Briefly, this pragmatic cluster-randomized trial evaluated the effects of temperature-reduced hemodialysis compared to standard-temperature hemodialysis on cardiovascular mortality and major cardiovascular events. Does it meet Harris' and Rhodes' criterion of having the prospect of generating socially and scientifically valuable knowledge?

Recall that socially valuable research is grounded in three factors: "the quality of the information to be produced, its relevance to significant health problems, and its contribution to the creation or evaluation of interventions, policies, or practices that promote individual or public health" (CIOMS, 2016, p.1). The MyTEMP trial was a well-designed study that aimed to reduce death and major cardiovascular events in patients on hemodialysis. The results of this study will directly inform hemodialysis policies in Ontario and may be applicable to other similar dialysis settings. Moreover, given that approximately 25% of patients receiving hemodialysis treatment in high-income countries die within a year of initiating treatment (Himmelfarb et al., 2020), almost 60% of Canadian patients on hemodialysis die within five years (CIHI, 2020), and the leading cause of death in this patient population is cardiovascular disease (Cozzolino et al., 2018), this trial meets Harris' and Rhodes' criterion of social and scientific importance.

According to the MyTEMP researchers, this trial also meets Harris' and Rhodes' risk criterion as, on their view, it posed no more than minimal incremental risk to participants. With respect to the interventions, patients whose facilities were randomized to provide standard-temperature hemodialysis were exposed to identical risks to those outside of the trial. The MyTEMP researchers also stated that the interventions were no more than minimal risk because they were "similar to a quality-control measure that could be implemented by a dialysis centre director" (Al-Jaishi et al., 2020b, Appendix 5). There were also no additional risks posed by data collection procedures, as baseline and outcome data were retrieved from routinely collected and anonymized administrative health care data.

Harris' (2005) third criteria is particularly relevant in this context: the research must be "in both personal and public interest" (p.245). According to Danielle Wenner (2017), for research to be in the public's interest, it must be "responsive to the health priorities of communities, seeking to ensure that studies have the potential to address important health deficits" (p.99). In 2019, there were almost 41,000 Canadians[14] living with end-stage kidney disease, and "the number of patients receiving dialysis nearly double over 20 years, from 11,601 in 2000 to 23,125 in 2019." (CIHI, 2020, p.4). Moreover, this disease disproportionately affects Indigenous peoples in Canada, who are nearly three times as likely as non-Indigenous patients to receive treatment (Collier, 2013). Providing maintenance hemodialysis treatment is also costly, averaging "$60,000 per patient per year when delivered thrice weekly (conventional) and even higher when delivered in shorter sessions daily or longer sessions nocturnally," and these treatments use "disproportionate resources relative to the size of the prevalent dialysis population and outcomes achieved" (Ferguson et al., 2020, p.20). Addressing this health disparity is evidently in the public's interest.

The requirement for research to be in the patients' own interest is limiting for most clinical research.[15] However, in the context of pragmatic cluster-randomized trials, patients who participate in clinical research like the MyTEMP trial may have some prospect of direct therapeutic benefit and, importantly, patients on hemodialysis—given how end-stage kidney disease is a chronic condition—are often the patients who will also benefit from the completion of the study. Even patients who receive kidney transplants may have recurrent kidney disease, or suffer from chronic organ rejection, or miss doses or stop taking their anti-rejection medication altogether, all of which will result in a return to dialysis (National Kidney Foundation, 2021). Thus, according to Harris and Rhodes' criteria, there would be a justified enforceable duty to participate in the MyTEMP trial.

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[14] Excluding Quebec citizens.

[15] For instance, phase I clinical trials test the safety, side effects, dosing, and timing of new treatments, and hence offer no prospect of therapeutic benefits for those who volunteer to participate. Participating in this research is likely not in the interest of many patients, although some may be interested in participating for altruistic reasons, for compensation, or to learn more about an illness.

2.2.2 Rejection of the social contract argument

The central claim underlying Harris' (2005) and Rhodes' (2005; 2017) social contract argument is that the enforceable moral duty to participate in clinical research is analogous to the enforceable duty to participate on a jury. Arguments by analogy are often used to demonstrate that an idea is worth taking seriously with the ultimate objective of persuading the reader to a certain point of view. On their view, if jury participation is analogous to research participation, and if there is a duty to participate on juries without consent, then there is a duty to participate in clinical research without informed consent. But the strength of an analogy largely depends on the number of morally relevant similarities between the two domains. The more differences, the weaker the analogy. This, I believe, is the first reason to reject their argument. There are at least two substantial and meaningful ways in which participating on a jury is different from participating in clinical research.

First, jury participation in Canada is required equally of all adult citizens, such that all citizens qua citizens are eligible to participate. Once called to participate, it is only a minority of individuals who will be found exempt. In contrast, clinical research evaluates the treatment of diseases and disabilities and, accordingly, those eligible for participation are those suffering from some illness. As a result, the duty to participate in clinical research is not incurred by citizens qua citizens; instead, it is incurred in virtue of one's illness. This places an additional burden on those suffering from disease and disability, while most of the population—namely, healthy individuals—would be exempt from fulfilling their duty.

Second, participating on a jury is an essential part of the Canadian judicial system because it allows every citizen accused of a criminal offense to be tried by a jury of one's peers. The judicial system would be fundamentally undermined if the duty to participate was only incurred by a subset of society, rather than comprised of a fair and equal representation of the population. Participation in clinical research is not an essential part of the Canadian health system in the same way since the health system would not be fundamentally undermined if those who participate were from a subset of society. Indeed, our current system relies on a subset of society (i.e., healthy individuals and those with

illnesses who volunteer for clinical research) and is nonetheless able to generate scientifically and socially valuable knowledge.

Therefore, one reason to reject Harris' and Rhodes' argument is the weakness of the analogy. But, for the sake of argument, we can assume that their argument is sound. Another way to reject their argument is to demonstrate that the operationalization of the duty would result in a problematic research system. So how would this duty be operationalized? Harris (2005) suggests that the research recruitment process should be modelled after the United Kingdom's process of selecting jurors.[16] He states:

> All British citizens between 18 and 70 are liable for jury service. They may be called, and unless excused by the court, must serve. This may involve a minimum of 10 days but sometimes months of daily confinement in a jury box or room, whether they consent or not. However, although all are liable for service only some are actually called. If someone is called and fails to appear they may be fined. Most people will never be called but some must be if the system of justice is not to break down. Participation in, or facilitation of, this public good is mandatory (p.244).

But if the research participant recruitment process is based on the jury selection process, this would result in a system that is inferior our current volunteer-based system.

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[16] What would the recruitment process for clinical research be in Ontario, Canada if modelled after our jury selection process? According to the Government of Ontario (2021), every year approximately 700,000 Ontario residents would receive a letter from the Ministry of Health indicating that they have been randomly selected from the Registered Persons Database under the Ontario Health Insurance Plan to be considered for inclusion in a "participant roll." Like a jury roll, it would be a list of potential research participants who would be eligible during the ensuing year to serve as a participant. Everyone who receives the letter would be required by law to accurately complete an accompanying questionnaire and return it within 30 days using a pre-addressed postage-paid envelope. Questionnaires would include queries regarding demographic, employment, and private health information. Completed questionnaires would be received and sorted for eligibility. Those who are eligible may receive another letter, called a summons, at any time for up to three years after completing the questionnaire. The summons would indicate a location, date, and time that each person would be required to attend as part of a "research panel." Like a jury panel, it would be a large group of prospective participants from whom one or more studies could be conducted. Prospective participants would have the opportunity to request a deferral or excusal at the time they receive a summons by providing any available documentation that supports their request. Whether selected for a study or dismissed, people selected to create a research panel would be ineligible for research service for the next three years.

The jury recruitment process is fair because it selects jurors from a pool of all citizens using a random lottery system. But not all citizens have an equal chance of being recruited into clinical research using a random lottery system because people do not have an equal chance of becoming sick. A random lottery system in this context fails to attend to the social determinants of health,[17] whereas our current volunteer system allows for anyone, regardless of income, education, and so forth to participate in clinical research.

Such a recruitment system also excludes people who are motivated to participate in research. We do not allow people who are motivated to participate in the judicial system to become jurors on their own accord. Similarly, people may be motivated to participate in research to meaningfully contribute to society, to improve the lives of future patients, to learn more about their illness, to receive specialized treatment, or to receive compensation. Regardless of their motivation, if a person is not randomly selected, they would not be allowed to participate.

Finally, this system would include people in research who are not motivated to participate. Consider that many people do not have an interest in serving on a jury. There are many websites that convey different ways to avoid jury duty—people can attempt to prove economic hardship, request deferrals or advancement of the date, use their student status, or even "say that you are quite sick, going out of town… [or] if you have young children, consider using them as an excuse" (WikiHow, 2019). Even if selected for a jury, these websites indicate further ways of being dismissed. In terms of clinical research, there will be those who attempt to render themselves ineligible and, if they are included without their consent, they would likely not be inclined to comply with the research protocol or adhere to the intervention to which they are randomized. If enough participants do this, it will undermine the researchers' ability to detect meaningful results from the study.

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[17] Social determinants of health are non-medical factors that can affect one's health, such as income, education, housing, gender, and race.

In sum, Harris' and Rhodes' argument fails for two reasons. Their analogy is only a strong as the similarities between the judicial and research system, and I have argued that these systems differ in substantial and meaningful ways. Moreover, I have argued that even if we take their argument to be sound, the operationalization of an enforceable duty will either be unjust (as the duty disproportionately burdens those will illness) or will result in a recruitment system that is worse than the current volunteer-based system.

2.2.3 The deontological argument

The second argument invoked to support an enforceable moral duty to participate in clinical research stems from Kantian deontological theory. Kant (2005) argued that the fundamental principle underlying our moral duties is a categorical imperative; a command applying to all rational agents unconditionally. The first formulation of Kant's categorical imperative is: "Act only on that maxim through which you can at the same time will that it should become a universal law" (p.81). Many commentators take this formulation of the categorical imperative as a decision-making procedure for moral reasoning. The procedure is as follows: formulate a maxim; recast that maxim as a universal law that applies to all rational agents; consider whether that maxim creates any contradiction in a world governed by this law; and, if no contradiction occurs, then ask whether a rational agent would *will* to act on that maxim (Johnson & Cureton, 2016).

Although Marquis (1983) dismisses the idea that patients have a moral duty to participate in clinical research, he believes that there are two ways to argue for a moral duty to participate in research. The first strategy is an appeal to a social contract, as outlined in the previous section. The second, however, involves an appeal to Kantian deontological theory as described above. Marquis gives an example of how someone might argue for a moral duty to participate in research grounded in Kantian theory. He beings by asking us to consider the maxim, "when offered the opportunity to participate in clinical research, I shall refuse" (p.46). Following the decision-making procedure, Marquis states that if this maxim were universalized then the research enterprise would come to an abrupt halt, hence no advancement in medicine and, consequently, everyone would be worse off. Since this is not something a person would rationally will, the "maxim is immoral and one has an obligation to act on its opposite" (ibid).

Marquis subsequently denies this line of argument by appealing to the second formulation of Kant's (2005) categorical imperative, "Act as to treat humanity, whether in your own or in that of any other, in every case at the same time as an end, never as a means only" (p.88). One reading of this formulation, presumably Marquis' (1983) interpretation, is that any activity that treats people as means to an end is immoral. In his words, "The second formulation forbids using people merely as means. Enrolling someone in a randomized clinical trial involves exactly that" (p.47). So, on his view, clinical research unavoidably treats people as a means to the end of scientific progress. As this would be contrary to the second formulation of the categorical imperative, there is no moral duty to participate in clinical research.

Marquis, however, fails to consider the complexities of Kant's second formulation. Another reading of this formulation is that it stipulates a less stringent requirement: do not treat people *merely* or *only* as a mean to an end, but as ends in themselves. This does not mean that we can never treat a rational person as a means to an end; rather, it means that it is permissible to treat a person as a means to an end only when this person is simultaneously treated as an end in themselves. On this interpretation, it is morally permissible for researchers to treat prospective research participants as a means to the end of scientific progress when the participants adopt the ends of research as their own. In this way they are not treated *merely* as a means to an end. Thus, one could argue that rational agents are duty-bound to participate in clinical research when not treated merely as a means to an end.

Rhodes (2008) picks up on the deontological argument above, which she expresses this as follows:

> We each should live our lives by taking responsibility for ourselves, in Kantian terms, as good rulers over ourselves. Looking into the future with awareness of the fragility of our bodies, we owe it to ourselves to take steps that would make it most likely that we could fend off disease and disability so as to retain our autonomy. Because biomedical research offers our best chance for achieving that

> end, and because we cannot will an end without also willing the necessary means to achieve it, we are duty-bound to participate (p.37-38).

Both Kantian arguments above stipulate that there is some type of duty to participate in clinical research, but they fail to clarify in what ways we are duty-bound. Marquis' argument engenders a strong picture for the role of informed consent insofar as patients who autonomously authorize their participation in research are adopting the ends of research as their own and thus are not treated merely as a means to some end. Rhodes' argument, however, can be shown to support an enforceable moral duty to participate in research.

Kant (2005) writes of two types of duties: perfect and imperfect duties. A perfect duty is one which "permits of no exception to the advantage of inclination," while imperfect duties can admit of exceptions (p.81). In other words, perfect duties are "strict injunctions turning every particular act that falls under these duties into a binding duty," (Statman, 1996, p.211) while imperfect duties "bind us in a much looser way, leaving ample room for personal discretion" (ibid). For example, a perfect duty to refrain from murder means that any particular act of murder is impermissible, while an imperfect duty to help others can be fulfilled at any time and in many different ways.

As demonstrated in section 2.1, if the moral duty to participate in clinical research admits of exceptions—i.e., if it is a *prima facie* duty that allows for individuals with countervailing considerations to refuse participation—then it fails to account for how we can proceed with socially valuable clinical research without the informed consent of prospective participants. Although Shapshay and Pimple (2007) have previously argued that the duty to participate in clinical research is an imperfect duty (i.e., rational agents have a moral duty to participate in research insofar as they should say "yes" when asked for their consent), what is required to resolve the conflict is an argument in support of a perfect duty to participate in research.

Kant's (2005) main example of a perfect duty to oneself is to refrain from suicide. He asks us to consider the maxim: "From self-love I adopt it as my principle to shorten my life when its longer duration is likely to bring about more ill than satisfaction" (p.81).

This maxim is inconceivable when universalized, as it creates a contradiction: reason urges the agent to both end and preserve life. Hence, this is a duty that admits of no exceptions; rational agents have a perfect duty to refrain from suicide so as to retain their autonomy.

To refrain from suicide is commonly depicted as a particular act that falls under the perfect duty of self-preservation. Another particular act that arguably falls under a perfect duty of self-preservation is the act of participating in clinical research, provided that the research prolongs one's life, preserves one's autonomy, or accomplishes both. In light of this, re-consider Rhodes' (2008) argument. She states, "we owe it to ourselves to take steps that would make it most likely that we could fend off disease and disability so as to retain our autonomy" (p.38). In other words, her first premise is that a rational agent has a perfect duty to oneself to fulfill a particular act that falls under a duty of self-preservation. She continues, "biomedical research offers our best chance for achieving that end" (ibid). In other words, her second premise is that the act of participating in (some) clinical research offers the best chance for self-preservation. Presumably, the research would have to aim at preserving one's own life or rationality. Thus, Rhodes concludes, "we are duty-bound to participate in research," (ibid) such that we have a perfect duty to participate in research that aims to preserve one's own life or autonomy. This argument can be schematized as follows:

P1: Rational agents have a perfect duty of self-preservation.

P2: If rational agents have a perfect duty of self-preservation, then any particular act that falls under this duty is enforceable.

P3: Participating in clinical research (that aims to preserve one's own life or autonomy) is a particular act that offers the best chance for achieving the ends of self-preservation.

C: Therefore, rational agents have an enforceable duty to participate in clinical research (that aims to preserve one's own life or autonomy).

Once again, a compelling case for this duty would be the MyTEMP trial (Al-Jaishi et al., 2020b). As previously stated, something particular to the chronic disease context, unlike most research contexts, is that the benefits of the knowledge gained by the completion of research often applies to both current and future patients, including those who participate. Thus, a person is acting to prolong their own life by participating in a well-designed hemodialysis study that seeks to reduce patient mortality. Moreover, a person is acting to preserve their autonomy by participating in these trials. Patients on hemodialysis are "at a greater risk of dementia and Alzheimer's disease diagnoses [and] older patients on hemodialysis who [are] diagnosed with dementia [or Alzheimer's disease are] subsequently at a twofold higher risk of death" (McAdams-DeMarco et al., 2018, p.1339). With the awareness of this prognosis, and because "we owe it to ourselves to take steps that would make it most likely that we fend disease and disability [that directly affects] our autonomy" (Rhodes, 2008, p.38), there is a perfect duty to participate in the MyTEMP trial and similar pragmatic cluster-randomized trials conducted in the hemodialysis setting.

2.2.4 Rejection of the deontological argument

The problem with Rhodes' (2008) deontological argument stems from the third premise. Rhodes states that it is because clinical research offers "our best chance" for achieving the ends of self-preservation that we have a perfect duty to participate in research. But why should we think that the best chance we have to retain or preserve one's own life or future autonomy is participating in clinical research? To enroll patients into clinical research requires that the study interventions are in equipoise; that is, it cannot be known prior to the conduct of research that one intervention is better than the other(s). Some research may offer a chance of self-preservation, but any chance of self-preservation relies on the results of the trial demonstrating a treatment to be effective. Indeed, given that the effectiveness of the treatment is only known after the completion of the trial, it is quite plausible that participating in research exposes people to treatments that result in harmful outcomes. That is, participating in clinical research—even if it aims to preserve one's life or autonomy—is a particular act that offers a chance for negatively impacting one's life and autonomy.

With respect to end-stage kidney disease, participating in pragmatic cluster-randomized trials like the MyTEMP trial is not a patient's "best chance" for achieving the ends of self-preservation. Life expectancy for patients on hemodialysis varies depending on many factors, such as a patient's other medical conditions, on how well they follow their treatment plan (e.g., attending dialysis appointments, taking prescribed medication, adhering to diets), and whether they receive treatment in low- or high-resource settings or in rural or urban areas. Patients on hemodialysis living in a rural area might have a better chance to preserve their own life simply by moving to an urban area rather than participating in clinical research in their current area. It is far from clear that participating in clinical research offers the best chance for preserving one's life or autonomy.

A more reasonable argument would suggest that rational agents have a perfect duty to accept medical treatments that are proven to preserve one's life or autonomy. For example, if there existed a vaccine to prevent the onset of dementia, Kant would say that we must take it given that receiving this vaccination against a life- and autonomy-threatening disease is a particular act that offers the best chance for prolonging one's life. However, this argument would only hold if the hypothetical vaccination was known to be the best (or most effective) treatment that has been proven to preserve one's life and autonomy. Again, given that the effectiveness of a treatment under evaluation in clinical research cannot be known prior to the start of the study, it cannot be guaranteed that it offers any chance (and definitely not the best chance) for achieving the ends of self-preservation.

A second objection to Rhodes' (2008) argument in support of a perfect duty to participate in clinical research is that there is an inconsistency between Kantianism and her argument. It is antithetical to Kantianism to suggest that we have an enforceable duty to participate in research as such a duty clearly prohibits people from adopting the ends of research as their own. In other words, a perfect duty to participate in research cannot be generated from the categorical imperative since it would treat people merely as a means to an end. While Marquis (1983) dismissed a duty to participate in clinical research for similar reasons, the difference here is that Marquis failed to consider that patients, through an informed consent process, can adopt the ends of research as their

own and therefore not be treated *merely* or *only* as a means to an end. But to make participation in research compulsory and consequently obviate the need for informed consent, as a perfect duty suggests, this would by definition treat people merely as a means to an end. Thus, there cannot be a perfect duty to participate in clinical research.

2.2.5 The consequentialist argument

At the outset of this chapter, I noted that the prevailing view about participation in clinical research is that the act of volunteering as a research participant is supererogatory. It is an act which is morally praiseworthy, but not morally blameworthy if someone refrains from participating. The prototypical example of a supererogatory act, to which participation in research is often compared, is a charitable donation. Donating some of one's own capital is regarded as an act of charity, and thus it is believed that there is nothing morally wrong with refraining from giving. However, if it can be argued that the prototypical example of a supererogatory act is, in fact, an enforceable moral duty, then there may be an analogous argument for why participation in clinical research should also be regarded as an enforceable moral duty.

In *Famine, Affluence and Morality,* Peter Singer (1972) proffers an argument that people have a moral obligation to donate to charity to aid those needlessly suffering and dying from poverty. His argument can be schematized as follows:

P1: Suffering and death are bad.

P2: If it is in our power to prevent something bad from happening without sacrificing anything of comparable moral importance, we have a moral obligation to prevent it.

P3: It is in our power to prevent suffering and death by donating to charities.

C: Therefore, we have a moral obligation to donate to charities.

Singer's (1972) argument begins with an intuitive assumption that "suffering and death from lack of food, shelter, and medical care are bad" (p.231). The second, more contentious premise is supported by a thought experiment. He asks us to imagine the

following: “if I am walking past a shallow pond and see a child drowning in it, I ought to wade in and pull the child out. This will mean getting my clothes muddy, but this is insignificant, while the death of the child would presumably be a very bad thing” (ibid).

The controversial nature of this analogy stems from Singer’s claim that neither geographical proximity to the child nor the quantity of individuals nearby obviates a person’s obligation to rescue the child. Singer (1972) states that “the fact that a person is physically near to us… may make it more likely that we *shall* assist him, but this does not show that we *ought* to help him rather than another who happens to be further away” (p.232). Hence, the proximity argument may only give us a reason for helping those near to us first; although Singer believes that “the development of the world in a ‘global village’” means that there is “no possible justification for discrimination on geographical grounds” (ibid).

Singer (1972) also claims that “the fact that there are millions of other people in the same position… as I am, does not make the situation significantly different from a situation in which I am the only person who can prevent something bad from occurring” (p.232). He concedes that it makes a psychological difference (e.g., one feels less guilty about doing nothing if others also do nothing), but to Singer there is no moral difference—everyone is wrong to do nothing. He states, “The result of everyone doing what he really ought to do cannot be worse than the result of everyone doing less than he ought to do” (p.234).

Finally, Singer’s third premise is an empirical claim. This premise is only true if there is sufficient evidence to demonstrate that donating to charities does in fact prevent suffering and death. He argues that there is sufficient evidence to suggest that donations to certain charities will prevent suffering and death, thus, given the truth of the other premises, Singer concludes that we have a moral obligation to donate to charity.

There are two ways to understand the enforceability of Singer’s (1972) conclusion. What he refers to as the “moderate version” of his argument is that we have a moral duty to prevent bad things from happening, limited only by a sacrifice of “something morally important” (p.241). The “strong version” of Singer’s argument

generates a moral duty to prevent bad things from happening, limited only by a sacrifice of something with "comparable moral significance" (p.241). Endorsing the strong version, he says that this view "does seem to require reducing ourselves to the level of marginal utility," defined as "the level at which, by giving more, I would cause as much suffering to myself or my dependents as I would relieve by my gift" (ibid). On this view, people are required to give as much money to charity to prevent the suffering and death of those living in poverty so long as they or their dependents do not end up in poverty.

I acknowledge that Singer (1993) advocates setting a lower standard in his later work because doing so "might actually result in more aid being given… it would mean that in order to do the maximum to reduce absolute poverty, we should advocate a standard lower" (p.245). Indeed, Singer (2002) states that "the one central point in all [his] writing on this topic, from 'Famine, Affluence and Morality' onward, has been that the failure of people in the rich nations to make any significant sacrifices in order to assist people who are dying from poverty related causes is ethically indefensible" (p.127). Yet my purpose here is to draw on the strong version of Singer's argument to generate a consequentialist argument in support an enforceable moral duty to participate in research. A corresponding argument based off the stronger version of Singer's argument can be schematized as follows:

P1: Suffering and death are bad.

P2: If it is in our power to prevent something bad from happening without sacrificing anything of comparable moral importance, we have a moral obligation to prevent it, limited only by a sacrifice of something with comparable moral significance.

P3: It is in our power to prevent suffering and death by participating in clinical research.

C: Therefore, we have a moral obligation to participate in clinical research, limited only by a sacrifice of something with comparable moral significance.

Consider the context of end-stage kidney disease where suffering and death are prevalent. Patients on hemodialysis experience a substantial amount of suffering; indeed, the most common side effects include hypotension (causing dizziness), abdominal and muscle cramps, anemia (causing weakness), bone disease, pericarditis (causing chest pains), high potassium levels (causing rhythm disturbances in the heart), amyloidosis (causing joint stiffness and pain), and depression (Mayo Clinic, 2021). Overall, "the majority of published data shows strong weakening of the QoL [quality of life] of patients receiving hemodialysis" (Dabrowska-Bender, 2018, p.581). Moreover, as previously stated, almost 60% of Canadian patients on hemodialysis die within five years (CIHI, 2020), often due to cardiovascular disease (Cozzolino et al., 2018). Death and suffering of this kind might also be prevented, or at least substantially reduced, if patients receiving hemodialysis participate in the MyTEMP trial. The question, then, is whether premise two is true: would patients sacrifice anything of comparable moral importance by participating in the MyTEMP trial? If not, patients have a moral duty to participate in it.

Singer explicates "without sacrificing anything of comparable moral importance" as "without causing anything else comparably bad to happen, or doing something that is wrong in itself, or failing to promote some moral good, comparable in significance to the bad thing we can prevent" (p.231). Recall that the investigators of the MyTEMP trial argued that participation would pose no more than minimal incremental risk to participants. The study interventions either pose identical risks to those outside of the trial, or patients may feel colder than they otherwise would. There are also no additional risks posed by data collection procedures, as data are retrieved from routinely collected and anonymized administrative health care. And given the substantial suffering and death of patients on hemodialysis, there is no sacrifice of comparable moral importance. Therefore, patients have a moral duty to participate the MyTEMP trial and other similar pragmatic cluster-randomized trials conducted in the hemodialysis setting.

2.2.6 Rejection of the consequentialist argument

One way to object to the consequentialist argument in favour of a moral duty to participate in research is to refute the second premise. Recall that the supporting argument for the second premise is the drowning child thought experiment. In the thought

experiment, a person can save the life of a child without sacrificing something with comparable moral significance. But once the child is saved, presumably this person has dispelled their duty as there is no one left to save. Likewise, if everyone donated enough money to alleviate global poverty, then surely after this goal is attained our obligation would lessen or dissipate altogether. In terms of research participation, "if there were enough (or a surplus) of research participants, the case for research participation as a moral obligation would be as weak as moral appeals for blood transfusion volunteers when there is (and will be) no blood shortage" (Rennie, 2011, p.43).

Singer (1972) responds to this sort of objection, stating that "this is not to deny the principle that people in the same circumstances have the same obligations" (p.234). He believes that, given the current context of global poverty, there is an obligation to donate. Given different circumstances, such as a world in which there was no poverty, than surely Singer would agree that our obligations would differ. Similarly, given the current state of global health, e.g., in 2017, chronic kidney disease resulted in 1.2 million deaths and was the 12th leading cause of death worldwide (Carney, 2020), the consequentialist would insist that there is a duty to participate in certain clinical research studies like the MyTEMP trial.

Yet the consequentialists argument heavily relies on the third premise; that it is in our power to prevent suffering and death by participating in research. The implicit consequentialist assumption is that the more people who participate in research, the greater the social benefits—better treatments, improved quality of life, and less preventable deaths. The argument is compelling to the extent that clinical research targets important global health problems and successfully implements the knowledge gained into clinical practice. However, the above assumption partly depends on empirical facts about how clinical research is conducted and implemented in clinical practice.

As expressed by Mark Yarborough (2017), those who tout the benefits of medical progress to support the moral duty to participate in research fail "to take into account all the consequences of [the research] system, both good and bad, when weighing claims that we are all obligated to support it" (p.328). He presents a summary of empirical evidence

(e.g., meta-analyses, systematic reviews, and seminal articles) that demonstrates the high failure rate of clinical research, and the amount of research that is wasteful, exploitative, and lacks significant value. Essentially, to say that it is in our power to prevent suffering and death by participating in clinical research fails to consider the steps between participation and the derivation of social benefit that are needed to make this premise plausible. Indeed, the evidence suggests that a duty to participate would result in a greater number of individuals being exposed to harms for little or no social benefit.

Another objection to the consequentialist argument is that the operationalization of the duty would result in a research system that allows for patients to be exposed to severe harm and even risks of death without their consent. Returning to the strong version of Singer's (1972) argument, people have a moral duty to prevent bad things from happening, limited only by a sacrifice of something with comparable moral significance (p.241). This argument, when reconstructed to apply to pragmatic cluster-randomized trials, is that if people could prevent the suffering and death of patients receiving hemodialysis by participating in the MyTEMP trial, then they are morally required to provided that those enrolled do not end up dying or suffering to a greater extent than other patients receiving hemodialysis. Since the incremental risks associated with participating in MyTEMP are minimal and there is substantial potential to develop and contribute to generalizable knowledge that can prevent death and major cardiovascular events of future patients, patients have an enforceable duty to participate.

But in the broader context of clinical research, this argument also permits the conduct of trials that pose substantial harm to healthy individuals without their informed consent, provided that those enrolled do not end up dying or suffering to a greater extent than those who are currently dying or suffering. For example, each year approximately 400 million people are infected with dengue fever (Rose & Sekhar, 2019). There are no antivirals for the disease and the only licensed vaccine is not widely used due to safety concerns (ibid). Controlled human infection model studies—trials in which a strain of an infectious agent is administered to healthy volunteers who are then closely monitored for evidence of infection and to anticipate or manage symptoms—are currently being used to assess the efficacy of novel vaccines in development for dengue (ibid). Although

participation may result in death and will in most cases result in participants suffering from the effects of the disease, participants enrolled in the study are provided with better medical care than those suffering and dying from dengue. Given that healthy individuals could prevent suffering and death from dengue by participating in these studies without their consent and since the sacrifice of harm and autonomy (though significant) is not of comparable moral significance, there would be a moral duty for people to participate in this type of research without consent—and surely that is not right.

In sum, the consequentialist argument for an enforceable duty to participate in clinical research fails for two reasons. The argument rests on the faulty assumption that the more people who participate in clinical research, the greater the social benefits. Second, a *reductio ad absurdum* argument demonstrates that the consequentialist argument would allow for any research, regardless of the harms posed to participants, to be conducted without consent provided that the prospect of social benefit is preventing the suffering and death of more people than those participating in the research.

2.3 Conclusion

In this chapter, I demonstrated that the debate about whether patients have a moral duty to participate in clinical research narrowly focuses on whether patients are morally required to accept when asked to participate. But since this *prima facie* duty cannot obviate a researcher's duty to obtain informed consent, I put forth the three strongest arguments based in three diverse philosophical origins in favour of an enforceable duty. Although pragmatic cluster-randomized trials in the hemodialysis setting, as exemplified by the MyTEMP trial, is one of the most probable contexts in which an enforceable duty would arise, I showed that each supporting argument for an enforceable duty succumbs to persuasive counterarguments. Therefore, barring any novel arguments, the first approach to resolve the conflict between respecting patient autonomy and the imperative to conduct pragmatic cluster-randomized trials fails. In the next chapter, I explore a second approach: the emerging practice of using a waiver of consent that permits the conduct of low-risk clinical research on patients without their informed consent.

Chapter 3: Using a waiver of consent to facilitate the conduct of pragmatic cluster-randomized trials

In the introductory chapter, I demonstrated that the conduct of pragmatic cluster-randomized trials is in tension with the requirement to obtain written informed consent from prospective research participants. The question this thesis seeks to address is whether the infringement on patient autonomy is justified by the imperative to conduct socially valuable clinical research. Those who took the first approach, discussed in the previous chapter, attempted to resolve the conflict by arguing that there is an enforceable duty to participate in clinical research. If such a duty exists, then the informed consent of patients need not be obtained. But each supporting argument for an enforceable duty could not be sustained. These arguments were unconvincing even in the hemodialysis setting, a compelling setting for which such a duty could arise. So, barring any new and convincing argument for an enforceable duty to participate in research, the first approach failed to resolve the tension in pragmatic cluster-randomized trials between the requirement to respect patient autonomy and the imperative to conduct socially valuable clinical research.

The second approach to resolve the tension in pragmatic cluster-randomized trials is the use of a waiver of consent. A waiver of consent can be granted by a research ethics committee if researchers prove that: "(1) the research would not be feasible or practicable to carry out without the waiver or modification; (2) the research has important social value; and (3) the research poses no more than minimal risk to participants" (CIOMS, 2016, p.37).[18] The use of a waiver of consent is an increasingly common practice for pragmatic cluster-randomized trials, and some researchers argue that "many low risk pragmatic trials assessing comparative effectiveness of commercially available medicines could fulfil the three provisions of the Council for International Organizations of Medical Sciences (CIOMS) ethical guidelines [for a waiver of consent]" (Dal-Ré et al., 2019, p.3). But the waiver of consent, including its component criteria, is undertheorized in the

[18] These three criteria in international research ethics guidelines are also consistent across national regulatory documents.

research ethics literature. In this chapter, I will focus on the question: can a waiver of consent be broadly used to facilitate the conduct of pragmatic cluster-randomized trials?

I begin, in section 3.1, with a brief history of the waiver of consent to demonstrate that its development was not intended to permit clinical research involving individual-level therapeutic interventions (i.e., interventions directly delivered to participants, such as prescribing drugs, physical activity regimens, or hemodialysis treatments to patients) without informed consent. Consequently, an explication of the underlying philosophical framework is required to know when, if ever, a waiver of consent is justifiable in pragmatic cluster-randomized trials that evaluate individual-level interventions. In section 3.2, I explore two frameworks—the rights-based framework and the presumed consent framework—that have been proposed as a philosophical foundation for the use of a waiver of consent. I enumerate flaws in both frameworks, and, in section 3.3, I advance a "specified principlism" framework as a promising foundation for a waiver of consent. The upshot of this framework is that the use of a waiver of consent in pragmatic cluster-randomized trials is permissible, but only in very limited circumstances. I thus conclude in section 3.4 that, without any other new and compelling frameworks, this approach fails to resolve the conflict between the requirement to respect patient autonomy and the imperative to conduct socially valuable pragmatic cluster-randomized trials.

3.1 The development of the "waiver of consent" in regulation

Prior to the Second World War, efforts to regulate research involving human participants were few and far between (Fluss, 2004). The Nuremberg Code (1947) is often considered the first modern ethics guidelines governing health research involving humans. Its first principle—"the voluntary consent of the human subject is absolutely essential"—established the requirement to obtain informed consent as a central ethical protection in research. All subsequent ethical guidelines for research involving human participants continue to uphold informed consent as a central ethical protection.

Due to the significance of obtaining informed consent for research participation, prominent research scandals often involved consent violations. For example, Henry Beecher (1966) published an exposé of twenty-two unethical studies conducted in the

United States between 1945 and 1965. Essentially, according to David Rothman's (1991) recapitulation of Beecher-as-whistleblower, all the studies "endangered the health and well-being of subjects without their knowledge or approval" (p.75). The Tuskegee Syphilis Study, spanning from 1932 to 1972, is arguably the most well-known example of unethical research in the United States. Researchers enrolled 600 African-American men (399 with syphilis, 201 without) in a study that aimed to record the progression of untreated syphilis. Although consent was obtained from participants, "there was no evidence that researchers had informed the men of the study purpose… Researchers told the men they were being treated for 'bad blood,' a local term used to describe several ailments, including syphilis, anemia, and fatigue" (CDC, 2020).

Public revelation of details of the Tuskegee study in 1972 lead to a United States Senate inquiry and a series of congressional hearings on biomedical and behavioural research involving human participants. The United States' government sought to prevent future unethical research; thus, in 1974 the National Research Act was signed into law. This Act created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (henceforth, the National Commission). The National Commission's task was to develop ethics guidelines for the conduct of biomedical and behavioural research involving human participants, to make recommendations for the application of their guidelines, and to explicate the underlying ethical principles. Their work was completed with the publication of the *Belmont Report* (National Commission, 1978a).

Over a span of five years, the National Commission released ten reports and additional appendices. Within these reports is where the modern notion of a waiver of consent and its criteria were initially developed. The National Commission's (1978b) report, *Institutional Review Boards*, is where the term "waiver" is first used to describe instances in which consent need not be obtained from prospective research participants. However, as stated by the members of the National Commission, "the protection of human subjects in federally funded research [was] far from uniform" (p.100). The term "waiver" did not have a settled technical meaning; references to it across various

regulatory documents encompassed what we now refer to as four distinct circumstances, only one of which is the modern conception of a waiver of consent.

For example, according to the members of the National Commission's (1978b) report, FDA regulations "permit a waiver of the consent requirement if the investigators 'deem it not feasible or in their professional judgment contrary to the best interests' of the subjects. This is explained as applying to cases in which (1) the communication of information to obtain consent would seriously affect the patient's well-being or (2) the patient is in a coma or is otherwise incapable of giving consent, his representative cannot be reached, and it is imperative to administer a drug without delay" (p.104). The first circumstance in which the term "waiver" was invoked is currently called "therapeutic privilege." The second circumstance is currently referred to as an "emergency exception to consent."

The third circumstance in which the term "waiver" was invoked is currently called "a waiver of documentation of informed consent." The members of the National Commissions (1978b) believed that the written consent form may pose risks to participants "in certain studies of illegal behavior or drug abuse," and in other studies that "may place an undue burden on the research while adding little protection to the subjects" (p.28); for example, telephone surveys and mailed questionnaires. Thus, they stated that a research ethics committee "may waive the requirement for documentation of consent in the interest of protecting the subjects" (p.28).

The circumstance that corresponds with the contemporary usage of a waiver of consent is found in the National Commissions' (1978b) recommendations within the *Institutional Review Boards* report. Recommendation (4)(H) states:

> Informed consent is unnecessary (i) where the subjects' interests are determined to be adequately protected in studies of documents, records or pathological specimens and the importance of the research justifies such invasion of the subjects' privacy, or (ii) in studies of public behavior where the research presents no more than minimal risk, is unlikely to cause embarrassment, and has scientific merit (p.21).

Plainly the members of the National Commission believed a waiver of consent should only be granted for two types of research: retrospective reviews of identifiable patient medical records or biospecimens, and for field research in the social sciences that present no more than minimal risk. In their comments on Recommendation (4)(H), the authors specify that granting a waiver of consent "must be essential to the methodological soundness of the research, and must be justified by the importance or scientific merit of the research" (p.30-31).

The reports and recommendations from the National Commission laid the foundation for the Common Rule, which is the current regulations in the United States that govern all research involving human beings (DHHS, 2022). The United States was among the first countries to create regulations specific to the review, approval, and oversight of research (Emanuel et al., 2011, p.157) and many countries, including Canada, based their informed consent requirements upon those within the Common Rule. In the 1981 United States research regulations, the criteria for a waiver of consent, based on Recommendation (4)(H) from the National Commission's (1978b) *Institutional Review Board* report, were as follows:

> (1) the research involves no more than minimal risk to the subject; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation (President's Commission, 1981, p.97-98).

The definition of minimal risk, which first appeared in the National Commission's (1978c) *Research Involving Those Institutionalized as Mentally Infirm* report, refers to "the risk (probability and magnitude of physical or psychological harm or discomfort) that is normally encountered in the daily lives, or in the routine medical or psychological examination, of normal persons" (p.8). The second criterion ensures that "subjects' interests are determined to be adequately protected" and the third criterion ensures that the waiver of consent is "essential to the methodological soundness of the research" (National Commission, 1978b, p.30-31). The fourth criterion refers to studies "where

participants have been deceived in the course of research," because, according to the members of the National Commission, "it is desirable that they be debriefed after their participation" (p.27).

Canada's Tri-Council Policy Statement, first promulgated in 1998, copied the United States' four regulatory requirements for a waiver of consent. However, the Canadian regulations added the following fifth requirement: "(5) the waived or altered consent does not involve a therapeutic intervention" (CIHR et al., 1998). The first revision to the Tri-Council Policy Statement occurred in 2010. One substantial change was the inclusion of a new section following the five criteria, called "Application," which described the circumstances in which a waiver of consent would be permissible. The only example provided was "social science research, particularly in psychology" (CIHR et al., 2010). Specific guidance for the secondary use of data (including retrospective review of medical records) and biospecimens was moved to Article 5.5.

While all five criteria need to be met for a research ethics committee to grant a waiver of consent, low-risk social science studies and retrospective review of medical records offer the clearest examples of when research is rendered impossible or impracticable if informed consent was required.[19] In some psychological studies, it is impossible to answer the scientific question if participants are aware of the true purpose of the study prior to its start. And while it is theoretically possible to obtain informed consent for retrospective review of medical records, it is impracticable insofar as it "would create expense and inefficiency without materially furthering the goal of showing respect for the patients whose records we examine" (Levine, 1986, p.147).

Two years after the revisions to the Tri-Council Policy Statement, the first and only comprehensive ethics guidance document specific to cluster-randomized trials—the *Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials*—was

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[19] Impracticable is defined as "a degree of hardship or onerousness that jeopardizes the conduct of research" (CIHR et al., 2018). It can be impracticable in a variety of ways (e.g., for logistic, practical, or economic reasons) to conduct research with informed consent, but it was the potential to undermine the "methodological soundness of the research" that the National Commission (1978b) was originally concerned about.

published (Weijer et al., 2012). This guidance document identified seven ethical issues and set forth fifteen recommendations for addressing the issues posed by cluster-randomized trials. One of the ethical issues identified pertains to the difficulties associated with obtaining informed consent in cluster-randomized trials.

The difficulties in obtaining informed consent in cluster-randomized trial have been linked to the level of the intervention under evaluation. Edwards and colleagues (1999) distinguish between cluster-level interventions and individual-level interventions. Cluster-level interventions are indivisible at the individual level, such as "promoting lifestyle changes on local radio;" whereas individual-level interventions are directly delivered to individual participants, such as a "cluster trial of a routine vaccine versus an experimental vaccine" (p.1407).

The emerging consensus in the literature promotes an expanded use of a waiver of consent for cluster-randomized trials evaluating cluster-level interventions (Edwards et al., 1999; Eldridge, Ashby & Feder, 2005; McRae et al., 2011; Sim & Dawson, 2012). According to these commentators, since cluster-level interventions affect whole clusters of people, "individuals cannot therefore decide or act independently" (Edwards et al., 1999, p.1408) and "there is little or no scope for any individual community member to opt out (although individual consent may feasibly be given or withheld for outcome assessment or access to health records)" (Sim & Dawson, 2012, p.481).

The Tri-Council Policy Statement was replaced in 2014 with the Tri-Council Policy Statement 2 due to substantial revisions. Notably, the fifth criterion for a waiver of consent was removed. It is unclear why those involved in the revisions removed this criterion; however, the section on "Application" was expanded upon, thus providing some insight. The examples in which a waiver of consent was thought to be permissible included low-risk social science research, research involving the continued use of data or human biological materials, and for "some population and public health studies… For example, a cluster-randomized trial comparing the efficacy of two different stop smoking campaigns in two or more communities… [or] comparing the effectiveness of different types of water treatment facilities" (CIHR et al., 2014). Clearly, the use of a waiver of

consent was thought to be permissible for certain public health studies; specifically, cluster-randomized trials evaluating cluster-level interventions.

The Council for International Organizations of Medical Sciences' *International Ethical Guidelines for Health-research Involving Humans* were most recently revised in 2016, adding specific recommendations for obtaining informed consent in cluster-randomized trials. These recommendations are also aligned with those provided in the *Ottawa Statement*. The CIOMS (2016) international ethical guidelines state:

> As a general rule, researchers must obtain informed consent from participants in a cluster randomized study unless a waiver or modification of consent is granted by a research ethics committee. Waivers or modifications of informed consent may be necessary in some cluster randomized trials in which it is virtually impossible to obtain individual informed consent. This occurs when the intervention is directed at an entire community, making it impossible to avoid the intervention. Examples include a study comparing methods of incinerating waste or fluoridating the drinking-water supply to prevent dental carries. Members of the intervention community cannot avoid being affected by the intervention, so obtaining individual informed consent is impossible (p.79).

In sum, the creation and development of the waiver of consent demonstrates its purpose was to permit the conduct of (1) retrospective review of medical records with adequate privacy and confidentiality protections, (2) research in the social sciences that posed no more than minimal risk, and (3) public health cluster-randomized trials evaluating cluster-level interventions.

However, the use of a waiver of consent is an increasingly common practice for pragmatic cluster-randomized trials that evaluate individual-level therapeutic interventions. A recent systematic review of 103 pragmatic or comparative effectiveness trials performed at least in part in the United States and published in 2014 and 2017 found that 23 (22%) of the trials were done with a waiver of consent (Lin, Jochym & Merz, 2020). In our recent systematic review of all cluster-randomized trials in the hemodialysis setting published between 2000 and 2019, 13% reported a waiver of

consent—all involved individual-level therapeutic interventions (Al-Jaishi et al., 2020a). In our other review of a random sample of 40 cluster-randomized trials evaluating individual-level therapeutic interventions, 20% reported a waiver of consent (Taljaard et al., 2020). If these trials were individually randomized, as opposed to cluster randomized, many of these would be standard drug trials in which patients' informed consent would be necessary. Indeed, the CIOMS (2016) guidelines state that for cluster-randomized trials that evaluate individual-level interventions, "individuals may be able to consent to the intervention before it is administered in that cluster. For example, parents will not be able to consent to their children's school being randomized to a vaccination programme or to being allocated to that cluster, but they could consent or refuse to consent to their child's vaccination at school" (p.80).

Given that regulations were not created with pragmatic cluster-randomized trials of individual-level therapeutic interventions in mind, this raises the focal question of this chapter of whether a waiver of consent should be broadly used to facilitate the conduct of these trials. Is the use of a waiver of consent ethically justifiable for this purpose?

3.2 Philosophical frameworks for a waiver of consent

Neither regulatory nor ethics guidance documents provide a general justification for the use of a waiver of consent. As was demonstrated in the previous section, the development of the waiver of consent was meant to permit a narrow set of research activities, including retrospective review of medical records, low-risk social science studies, and public health cluster-randomized trials evaluating cluster-level interventions. To know whether it is permissible to use a waiver of consent for other types of research—specifically, pragmatic cluster-randomized trials evaluating individual-level therapeutic interventions—an explication of the underlying philosophical framework is needed. As stated in the introduction to this chapter, two plausible philosophical frameworks have been proffered to justify the use of a waiver of consent: the rights-based framework and the presumed consent framework. In what follows, I explicate both frameworks and argue that neither is persuasive.

3.2.1 Rights-based framework

Gelinas and colleagues (2016) posit a rights-based framework to ground the conduct of research with a waiver of consent. Their framework comprises two interrelated criteria: research without consent is permissible "either when research stands to infringe no rights of research participants… or when the expected social value of research that does infringe on participant rights outweighs the gravity of the minor rights infringement" (p.37). They also claim that obtaining consent must be impracticable; that is, "obtaining consent imposes (prohibitively) high costs of time or economic resources on researchers or that obtaining consent threatens the scientific validity of the research, as might happen when getting consent threatens to introduce certain kinds of selection bias into the study" (p.36). They continue, "The reason consent must, on either justification, be impracticable for it to be justifiably waived is that, in general, obtaining consent helps to promote transparency and trust in the research enterprise" (ibid).

Gelinas and colleagues' (2016) argument begins with the claim that there are two purposes of informed consent. First, they say, "the primary function of informed consent in human research is to protect autonomy," where autonomy is defined as possessing "rights that grant [people] a sphere of personal control over [their] life and decisions" (p.36). The secondary function of consent is "to protect and advance the interests of prospective research participants" (ibid). This is based on the idea that "people will typically consent to something only if they believe that doing so advances their interests" (ibid).

On Gelinas and colleagues' (2016) view, the two functions of informed consent are separable. For example, they say, "Tom may set back Mary's interests when he buys the last seat at a concert that Mary was hoping to see or declines to interview Mary for a job she wants, but he does not violate Mary's rights" (p.36). Similarly, the authors suggest that patients have a right to refuse medical treatment and research participation, even if receiving the medical treatment or participating in research would serve their interests. Thus, they believe that a waiver of consent is permissible when no rights of the participants involved are infringed upon, regardless of whether they have or express an interest in research participation. Indeed, they surmise that:

> The most basic function of consent is to waive rights of control, allowing others to interact with us in ways that would otherwise be wrong. Consent is needed when, and only when, interactions stand to wrong one of the parties involved, by violating their personal sovereignty or rights of control (ibid).

Gelinas and colleagues (2016) ask us to consider "purely observational research regarding human behavior in a public place" (p.36). On their view, a waiver of consent is permissible because, even if the observational study violates someone's interest in not being observed for the purpose of research, it does not violate any rights of control and obtaining consent would render the research impracticable. However, there are cases in which the use of a waiver of consent would violate participants' rights. Gelinas and colleagues state, "If including someone in research without consent violates a right, it must be… the right not to be subject to bodily intrusion without one's informed consent." (ibid).

So, according to Gelinas and colleagues (2016), what justifies the use of a waiver in cases where rights are infringed? They say, "rights are not absolute, and certain types of infringements on rights can easily be outweighed by competing considerations, including the promoting of social good" (p.37). They provide an example of trespassing on private land to save the life of a person in need of immediate rescue. They continue, "In a similar fashion, minor rights infringements of research subjects can, we think, be justified for the sake of generating socially valuable knowledge" (ibid).

Consider the MyTEMP trial (see Textbox 1). Recall that a waiver of consent was granted for this pragmatic cluster-randomized trial wherein patients were provided either temperature-reduced dialysis (0.5ºC to 0.9ºC below each patient's body temperature) or standard-temperature dialysis (36.5ºC) depending on the protocol assigned to their cluster. Was the use of a waiver of consent in the MyTEMP trial justified? According to Gelinas and colleagues (2016), a waiver of consent is justified only if (1) the rights infringement is minor, (2) the infringement is outweighed by the expected social value, and (3) obtaining consent would render the research impracticable.

First, Gelinas and colleagues (2016) believe that a waiver of consent is permissible for "cluster randomized studies that involve aspects of care over which institutions, not patients, hold a right of control" (p.39). Specific details about hemodialysis treatments, including the temperature at which hemodialysis is provided, are not disclosed in the clinical consent process; a patient's dialysis temperature is often decided by the treating nephrologist or occasionally set as a local policy. Indeed, the MyTEMP researchers considered the interventions to be "similar to a quality-control measure that could be implemented by a dialysis centre director" (Al-Jaishi et al., 2020b, Appendix 5). Given what occurs in the clinical setting, Gelinas and colleagues are likely to conclude that the bodily intrusion that occurs when modifying patients' hemodialysis temperature is not within the patients' right of control, amounting to a minor infringement on their right to bodily integrity.

Second, if you agree that the infringement on patients' right to bodily integrity is minor, then it must be argued that the infringement is outweighed by the expected social value. Again, the expected social value is substantial for both current and future patients, as well as health providers and health system managers. Recall that about 25% of patients die within the first year and almost 60% die within five years of initiating hemodialysis, often from cardiovascular complications. The MyTEMP trial aims to help reduce mortality and major cardiovascular events. Moreover, due to the pragmatism of the trial, the results should provide robust evidence that can be swiftly and cost-effectively integrated into the clinical setting in Ontario, Canada, and will be generalizable to other similar clinical settings.

Finally, to obtain informed consent from over 15,500 patients at 84 clinics over four years would impose prohibitively high costs of both time and economic resources on researchers. Even if the costs were not prohibitively high, the aim of pragmatic trials is to integrate research into real-world clinical settings to maximize external validity at minimal cost. Devoting additional resources, such as hiring additional staff to recruit patients, and deviating from routine clinical practice are both contrary to the aims of pragmatism. Therefore, the rights-based framework can justify the use of a waiver of consent for the MyTEMP trial.

3.2.2 Problems with the rights-based framework

Gelinas and colleagues (2016) provided two arguments for their framework, one argument in support of each criterion. Their first argument explains why a waiver of consent is justified when no rights are infringed upon. They start with the claim that the purpose of informed consent is to protect the autonomy of research participants, where autonomy is defined as possessing rights of control over one's life and decisions. They correctly believe that autonomous people have a right of control over their bodies, hence why they state that including someone in research without consent violates "the right not to be subject to bodily intrusion without one's informed consent" (p.36). They conclude that if no rights are violated in the conduct of research, then a waiver of consent is justified.

But Gelinas and colleagues (2016) construe the need to protect autonomy too narrowly as the need to protect the right to bodily integrity. Rather, the ethical principle of respect for autonomy means that "individuals should be treated as autonomous agents" (National Commission, 1978a, p.4). To treat people as autonomous requires that prospective research participants "to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them," (p.10) and this principle also provides the "ethical grounding for the requirement to respect the privacy of persons… we must respect the individual's autonomy regarding personal information" (Levine, 1986, p.163).

To reiterate in the jargon used by Gelinas and colleagues (2016), respect for autonomy gives rise to, at least, two rights: the right to bodily integrity and the right to privacy. Thus, even if research does not involve bodily intrusion, patients have privacy rights that may be undermined. For example, patients provide private demographic and medical data in clinical practice under the presumption that it will be kept confidential and only used to further their own health outcomes. Some prospective observational studies, such as those that involve the review of medical records, would infringe upon patients' privacy rights if they were conducted without informed consent. Empirical work demonstrates that few people would permit researchers access to their medical records

without informed consent, even if researchers could guarantee the advancement of medical knowledge (Kass et al., 2003).

Broadening the scope of "rights of control" to include both bodily integrity and privacy poses a relatively minor problem with the rights-based framework. If we accept the argument that people have a right to bodily integrity and health information privacy, then there will simply be very few cases in which criterion one of Gelinas and colleagues' (2016) framework obtains. The only example that plausibly meets this criterion would be their example of "purely observational research regarding human behavior in a public place" (p.36). All this means is that most, if not all research (including many observational studies) cannot proceed with a waiver of consent unless Gelinas and colleagues' second criterion obtains: a waiver of consent is justified when the rights infringement is minor and outweighed by the prospective social value.

The argument in support of the second criterion relies on the claim that all rights are not absolute; it must be the case the rights can trade-off against one another. Gelinas and colleagues' (2016) example of trespassing on private land to save someone's life aims to push our intuitions towards accepting that rights are not absolute (p.37). However, Alan Gewirth (1981) has argued that "agents and institutions are absolutely prohibited from degrading persons, treating them as if they had no rights or dignity" (p.16). He continues, "other specific absolute rights may also be generated from this principle" (ibid). His examples include the right not to be tortured and the right not to be made the intended victim of a homicidal project. It may be argued by extension that the right to be free from research without informed consent is absolute. In fact, the United Nations considers this right to be absolute. Article 7 of the United Nations' (1976) *International Covenant on Civil and Political Rights* treaty states:

> No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation.

But, for the sake of argument, if we grant Gelinas and colleagues (2016) that the right to be free of research without informed consent is not absolute, the next premise of

their argument is that patients' rights can be outweighed by the expected social value of the research. As I argued above, Gelinas and colleagues would likely consider the bodily infringement in the MyTEMP trial as an example of a minor rights infringement that is outweighed by the expected social value.

However, Gelinas and colleagues would be wrong think that modifying a patient's hemodialysis treatment without their informed consent for the purposes of research constitutes a minor infringement on bodily integrity. Running reduced-temperature dialysate directly into a patient's vein—which can result in unpleasant shivering for the entire treatment duration—without informed consent is a non-trivial infringement on bodily integrity. Patients often experience unpleasant shivering during normal dialysis treatments. Indeed, participants involved in a recent qualitative study (involving focus groups and interviews with patients on hemodialysis and their caregivers) expressed concern about the lack of availability of blankets during dialysis sessions (Sass et al., 2020, p.5). One participant stated, "Yes, definitely we need the warm blankets. I don't think I can do dialysis without the warm blankets" (p.8). Reducing the temperature of hemodialysis treatments by 0.5 to 0.9°C would exacerbate discomfort to the extent that patients may consider stopping their life-sustaining treatment. Thus, alterations to a patient's hemodialysis treatment in this way is a non-trivial infringement on their bodily integrity.

Moreover, while specific details regarding hemodialysis are not disclosed in the clinical consent process, the current informed consent process for dialysis often falls short of ethical and legal requirements (Brennan et al., 2017; Li & Brown, 2020). Patients are often provided less information than required to provide voluntary and informed consent to clinical dialysis care, and empirical evidence suggests that the "vast majority of nephrology patients want to be given as much information as possible, good or bad, including prognosis" (Brennan et al., 2017, p.1003; see also Fine et al., 2005). It is not sufficient to rely on common practice as a means of qualifying the modification of a patient's hemodialysis treatment without their informed consent as a minor rights infringement.

It is also unclear why the rights infringement, whether major or minor, can be overridden by the expected social value of clinical research. Gelinas and colleagues (2016) posited that rights can trade-off against one another. Their example: the right to life can override property rights in certain circumstances. They did not argue that rights can be infringed upon by the promise of advancing medical knowledge. We could charitably interpret "the expected social value of research" as "the rights of future patients," which would mean that a waiver of consent is justified when the rights of future patients outweigh the rights of current patients. But the rights of current patients override the ill-defined rights of future patients. Consider the causal uncertainty between the conduct of research and fulfilling the rights of patients. Resource waste is an issue in all areas of research, but more so in nephrology where "billions of dollars have been spent on kidney disease research in the past decades, with no tangible progress in clinical practice" (Yaseen et al., 2019, p.69). The lack of tangible progress is due to the number of randomized controlled trials published in nephrology—which is lower than that in other medical subspecialties—and because most of the larger clinical trials in nephrology yield negative results (ibid). Even if it could be argued that future patients have some *prima facie* right to advances in nephrology practice, there is no guarantee that these advances will be achieved by overriding the right to bodily integrity of current patients.

3.2.3 Presumed consent framework

A second framework considers a waiver of consent to be a species of presumed consent. In other words, the use of a waiver of consent is justified if there are strong reasons to believe that participants would agree if they were asked and capable of providing informed consent. Two arguments have been proffered to support this framework. Francis Baker and Jon Merz (2018) provide an argument grounded in the legal doctrine of privilege, while Scott Kim and Franklin Miller (2016) provide an argument grounded in the ethical principle of respect for autonomy.

According to Baker and Merz, the legal requirement to obtain informed consent is based on the principle, succinctly stated by Judge Cardozo, that "every human being of adult years and sound mind has a right to determine what shall be done with his own body" (Schloendorff v. Society of New York Hospital, 1914). This means that if a

physician provides a medical or surgical treatment to a patient without their consent, this amounts to a case of battery (Baker & Merz, 2018, p.580). Or if a physician fails to adequately inform the patient when consent is sought, this amounts to a case of negligence (ibid).

Due to concerns of battery and negligence, is informed consent always required to provide medical or surgical treatment? Baker and Merz (2018) state that the legal doctrine of privilege provides insight on when informed consent need not be obtained:

> Privilege provides an affirmative defense to a *prima facie* tort such as battery, assault, or trespass. If a defendant can show that either she has the plaintiff's consent or she was acting in furtherance of a goal of sufficient social importance, then privilege will insulate her from liability for the plaintiff's damages (p.580).

In clinical practice the notion of privilege allows for health providers to administer emergency treatment to incapacitated patients at risk of death or serious bodily harm without their consent. In Baker and Merz's (2018) view, privilege only provides an affirmative defense when it is "reasonable to believe that most people in an emergent condition, such as immediately after being in a serious car accident, would agree to medical care for their injuries" and there is "no evidence that the individual patient would not have wanted to be treated under the circumstances" (p.580). Thus, when these conditions are met, medical treatment can be administered without seeking consent.

Baker and Merz (2018) also believe that the notion of privilege underlies the conduct of research without informed consent. They appeal to a statement by the Food and Drug Administration (FDA) on their regulations governing the *Exception from Informed Consent Requirements for Emergency Research* (21 CFR 50.24). They claim that the FDA "would not consider writing a rule that would permit the waiver of informed consent in a situation where if consent were requested, it would be refused" (p.580). Thus, Baker and Merz conclude that the notion of privilege underlies the conduct of emergency research without informed consent.

Since "the right to consent extends beyond trials run in emergency settings to other interventional or experimental studies," (p.580) Baker and Merz (2018) assert that "the ethical and legal legitimacy of the privilege to provide standard of care treatment or *to waive consent for research* is predicated upon the reasonable belief that potential subjects would agree if they were asked and capable of consent" (ibid, italics added). They suggest that a simple majority is appropriate for the least intrusive research (e.g., "the secondary analysis of blood samples"), but for clinical research "there must be good evidence that the overwhelming majority of individuals who would be enrolled would agree, if asked" (p.583).

Kim and Miller's (2016) argument stems from the ethical (rather than legal) foundation of informed consent: respect for autonomy. They begin by suggesting "it is possible to show respect in ways other than obtaining informed consent" (p.2). They state that respect for autonomy "also encompasses trust, transparency, and considerations of other legitimate expectations that arise from relationships between clinicians and patients and between clinical investigators and research participants" (ibid). Thus, on their view, any alternative to informed consent that lacks trust and transparency "does not give individuals any opportunity to directly authorize their participation in research" (p.3). Kim and Miller posit that—when trust and transparency are both present—a waiver of consent can conform to the principle of respect for autonomy.[20] It does so when each of the criterion that must be met to grant a waiver of consent conforms with the principle of respect for autonomy to the greatest degree possible. Using the criteria outlined in the United States' Common Rule, Kim and Miller demonstrate how the criteria conform to respect for autonomy. Note that Kim and Miller use the pre-2018 Common Rule criteria for a waiver of consent (see Textbox 2).

[20] It may seem oxymoronic to say that a waiver of consent, which means that patients are not approached for their informed consent, can be consistent with transparency, which means that patients are made aware of ongoing clinical research. However, patients can be made aware of ongoing research using notification strategies, e.g., posters or pamphlets, when a waiver of consent is granted by a research ethics committee.

Textbox 2: Common Rule pre-2018 requirements for a waiver of consent.

> "An IRB [Institutional Review Board] may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:
>
> (1) The research involves no more than minimal risk to the subjects;
> (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
> (3) The research could not practicably be carried out without the waiver or alteration; and
> (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation." (DHHS, 2009).

First, Kim and Miller (2016) state that the minimal risk criterion "is used to set the risk threshold above which no alternative to regulatory consent is compatible with respect for persons" (p.3). This criterion relies on the implicit claim that most patients would not agree to be exposed to more than minimal risk without their informed consent. Second, the rights and welfare criterion requires research ethics committees to ask whether "participants [would] object to the waiver or consider that [the] waiver has potential to cause adverse consequences for them" (p.4). As Baker and Merz's (2018) suggest, researchers must demonstrate that an overwhelming majority of participants would agree to participate if they were asked and capable of providing informed consent. Third, the impracticability criterion requires research ethics committees to judge whether the research would be impossible or impracticable if consent was required, and whether any alternative model of consent could be implemented prior to granting a waiver of consent. The implicit empirical premise is that patients, when given the option, generally prefer to be asked for their informed consent. Finally, the criterion of providing additional pertinent information to patients when possible (e.g., using posters, letters, or other media) is a way to ensure trust and transparency are maintained throughout a study.

With the presumed consent framework in mind, consider the following: can a waiver of consent be used to facilitate the conduct of pragmatic cluster-randomized trials? Returning to the MyTEMP trial (see Textbox 1), the research ethics committee responsible for granting the waiver of consent agreed with the researchers' determination that the study met the criteria for a waiver. However, the investigators did not demonstrate that the overwhelming majority of patients receiving hemodialysis

treatments in participating facilities would have agreed to participate, if asked. In other words, the rights and welfare criterion for a waiver of consent did not obtain.

According to Baker and Merz (2018), "waivers should be rare and based on much more explicit input… among the target population" (p.584). Their scoping review found that "many people—an average rate roughly on the order of 30%—do not take part in research when asked" (p.582). They point out that "a number of [other] studies have asked people about the acceptability of waivers in [pragmatic] trials, and a consistent majority favor consent in some form to outright waivers" (p.584). Thus, pragmatic cluster-randomized trials, generally, cannot proceed with a waiver of consent.[21]

3.2.4 Problems with the presumed consent framework

The presumed consent framework relies on the legal and ethical foundations provided by Baker and Merz (2018) and Kim and Miller (2016) respectively. Baker and Merz show how the legal doctrine of privilege underlies the exception to informed consent for emergency treatment in clinical practice and for participation in research evaluating emergency treatment. But they fail to provide an argument for why privilege underlies the waiver of consent in non-emergency settings—they merely assert that this should be the case. The problem with this assumption is that it conflates the exception to informed consent in emergency settings with the exception in non-emergency settings.

Privilege can only be invoked in a particular circumstance; specifically, when a patient is *incapable* of providing informed consent and requires *immediate intervention* without which they may *die or sustain serious injury*, and there can be *no evidence* that the patient would refuse the intervention if asked. As Baker and Merz (2018) correctly claim, these criteria are often met in the emergency clinical setting and for research evaluating emergency medical interventions. However, most circumstances in clinical practice and research do not share these features. In the non-emergency clinical and research settings, patients can provide informed consent or, if incapable, the lack of life-

[21] Further empirical work could be conducted to determine whether the hemodialysis setting presents a unique case where an overwhelming majority of patients would consent, if asked. However, we should not treat the absence of research as evidence that no one would object to the use of a waiver.

threatening urgency provides ample time to approach their legal representatives for consent. Thus, privilege cannot be invoked as a defense against battery and negligence in non-emergency settings.

Moreover, privilege does not provide a reason why a waiver of consent can be justifiably used in the non-emergency setting. For example, waivers of consent are permitted for retrospective review of medical records even though patients may be capable of providing consent for the use of their records, there is no urgency to conduct the review, and there is no treatment being administered to patients. As discussed in the previous section of this chapter, the waiver of consent was developed, in part, to permit the conduct of low-risk social science research in which patients or their legally authorized representatives may be capable of providing informed consent, but "non-disclosure [is deemed] essential to the methodological soundness of the research" (National Commission, 1978b, p.6). In these cases, it is not that patients are incapable, or their representatives are unreachable; rather, it is impracticable to obtain consent due to scientific considerations.

The case of *Halushka v. University of Saskatchewan* (1965) provides further evidence that privilege cannot be invoked as an affirmative defense in the conduct of non-emergency research.[22] In determining what constitutes an "informed" consent, Justice Hall claimed that physicians have a duty to provide a fair and reasonable explanation of the proposed treatment, including anticipated and probable side effects and risks. He continued, "There can be no exceptions to the ordinary requirements of disclosure in the case of research as there may well be in ordinary medical practice… The example of risks being properly hidden from a patient when it is important that he should

[22] The defendants involved in the case of *Halushka v. University of Saskatchewan* (1965) were conducting an experiment involving an anesthetic drug, fluoromar. Halushka, a student at the time, was offered $50 to participate in the study. He agreed after being told the experimental drug was safe and that numerous experiments involving this drug had been conducted. However, fluoromar was a new drug and was being tested for the first time, and Halushka was not informed about the risks of the drug or the study procedures. As a result of participation, Halushka went into cardiac arrest and was unconscious for four days, followed by ten days of in-hospital recovery. He was unable to return to university due to concentration problems and fatigue. The jury found the defendants guilty of battery and negligence. The court acknowledged that there are exceptions to informed consent requirements when it comes to clinical treatment (i.e., privilege), but these exceptions do not hold in cases of experimentation.

not worry can have no application in the field of research. The subject of medical experimentation is entitled to a full and frank disclosure of all the facts, probabilities and opinions which a reasonable man might be expected to consider before giving his consent" (ibid). Justice Hall clearly sets the precedent that privilege cannot be invoked as a defense in non-emergency research settings. Thus, due to the aforementioned reasons, the legal argument fails to support the presumed consent framework.

Kim and Miller's (2016) argument aims to support the presumed consent framework by grounding a waiver of consent in the principle of respect for autonomy. They correctly claim that respect for autonomy is operationalized by obtaining informed consent. However, they also claim that trust and transparency must be present for a person to autonomously authorize their participation in research. The latter claim means that people cannot make an autonomous decision to participate in clinical research in the absence of trust and transparency. Thus, on their view, trust and transparency are necessary conditions of respect for autonomy. And since, on their view, a waiver of consent conforms to the principle of respect for autonomy and a waiver of consent, by definition, does not provide prospective participants the opportunity to authorize their participation in clinical research, trust and transparency must also be jointly sufficient conditions of respect for autonomy.

The problem with Kim and Miller's (2016) arguments is that trust and transparency are neither necessary nor jointly sufficient conditions of respect for autonomy. If they were necessary, then it would not be feasible for people to make autonomous decisions without the presence of trust or transparency. But people do. For example, when a person purchases a car from a seedy salesperson, they make an autonomous decision to purchase the car knowing the salesperson is untrustworthy.

People can also make autonomous decisions without complete transparency. If transparency requires a full disclosure of all the relevant facts, people could not autonomously decide to take medication without a complete knowledge of all possible side effects. And yet they do. Or consider psychological studies in which researchers tell prospective participants that the true purpose of the study is being withheld from them,

and people nonetheless decide to participate—is this not an autonomous decision? According to Benjamin Freedman (1975), "the informing of the patient/subject is not a fundamental requirement of valid consent. It is, rather, derivative from the requirement that the consent be the expression of a responsible choice" (p.35).

Moreover, if trust and transparency were jointly sufficient conditions of respect for autonomy, people would be able to make an autonomous decision without the act of making a choice. The absurdity of this claim ought to be self-evident. The act of making a choice is the *sine qua non* of making any decision. An autonomous decision requires that someone "makes choices, typically, on the basis of reasons, arguments, or beliefs—and that he remains open to the claims of reasons, so that further rational argument might lead him to change his mind… [and] that he can live with the consequences of his choices" (Freedman, 1975, p.35). If you dispense with choice, which occurs when a waiver of consent is used in clinical research, you dispense with autonomy—regardless of the presence of trust or transparency.

Without a foundation in ethics or law, the presumed consent framework fails to ground the use of a waiver of consent. But even if a novel foundation could be provided, a final problem with this framework is that it is overly restrictive. The presumed consent framework is comprised of a single criterion: the use of a waiver of consent is justified if participants would agree to participate if asked. Consequently, the justified use of a waiver of consent relies on patients' preferences. The reliance on patient preference leads to two troubling conclusions. First, a waiver of consent cannot be justifiably used for a retrospective review of medical records; a type of research in which its use is uncontroversial. According to the presumed consent framework, for a waiver of consent to be justifiably used we need to know: what evidence do we have to suggest patients would agree, if asked, to participate in research involving the use of identifiable medical records? A recent survey of 1,246 patients in two academic hospitals in the United States demonstrates,

> A total of 291 patients (23.4%) were willing to share all items with any researcher, whereas 46 (3.7%) were not willing to share any items. The remaining

> 909 (72.9%) were willing to share selectively, meaning that they wanted to share at least 1 item with at least 1 type of institution with a general preference toward sharing within the institution in which the patient received care, followed by sharing with researchers from non-profit institutions (Kim et al., 2019).

According to Baker and Merz (2018), a simple majority, which occurs when more people would consent than those who would refuse, might be adequate for medical record reviews. The results of the survey revealed that only 23.4% of patients were willing to share all the information in their medical records (Kim et al., 2019). Since a waiver of consent for identifiable medical records allows researchers to access all the information within the patient's records, there would need to be a simple majority of patients who are willing to share all the information in their medical records. Clearly, this is not the case.

The second troubling conclusion is that the presumed consent framework has no mechanism for determining whether patients' preferences are reasonable or unreasonable. Moreover, if patient preferences are unreasonable, we would nonetheless be required to adhere to them. For instance, people have expressed an unreasonable preference to have their informed consent obtained for the use of anonymized data (Willison et al., 2003). It is an unreasonable preference insofar as there are no plausible infringements on people's autonomy with the use of anonymized data as the data are in no way connected to an individual patient. But, as people have expressed this preference, the use of a waiver of consent would not be justified even for the types of research it was created to permit.

3.3 The specified principlism framework

Given the problems with the two existing frameworks, I propose a novel framework to ground the use of a waiver of consent. In what follows, I argue that the specified principlism framework is the most promising grounds for the use of a waiver of consent. This framework suggests that the criteria of the waiver of consent are a specification of the exceptional cases in which it is morally permissible for the imperative to conduct socially valuable clinical research to override informed consent requirements. In other words, the use of a waiver of consent is morally permissible when the

requirements of beneficence override the requirements of respect for autonomy in accord with specified conditions.

Specified principlism is a method for resolving ethical issues that arise in the biomedical and behavioural sciences. In the context of clinical research, specified principlism uses a set of basic ethical principles—e.g., beneficence, justice, and respect for persons—that generate various, non-absolute moral requirements. As stipulated in the National Commission's (1978a) *Belmont Report*, beneficence "requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research" (p.16); justice requires "there be fair procedures and outcomes in the selection of research subjects" (p.18); and respect for persons dually requires "that individuals [are] treated as autonomous agents, and… that persons with diminished autonomy are entitled to protections" (p.4).

The first requirement of respect for persons (i.e., respect for autonomy) is fulfilled when prospective research participants autonomously authorize their participation in research through an informed consent process. The principle of beneficence conflicts with respect for autonomy when socially valuable research cannot proceed if informed consent is required. When this occurs, our choices are to conduct the research without consent, thereby failing to demonstrate respect for autonomy; or to refrain from conducting research, thereby failing to abide by beneficence requirements. Neither seems appropriate.

What should be done when principles or their requirements conflict? Henry Richardson (1990) and David DeGrazia (1992) contend that specification can be used to resolve conflicts between principles and their requirements. This approach has also been endorsed by advocates of principlism, including Tom Beauchamp and James Childress (1979; 2019), and Robert Veatch (1995). When conflicts between principles or their requirements occur, the answer, according to DeGrazia (1992), "is to tailor one of the norms to make it more specific" (p.525). John Arras (2017) further describes the process of specification as follows:

> Initial abstract formulations of principles will become increasingly concrete, specified, and delimited as one approaches the level of the particular case. Thus, what begins as a straightforward abstract principle (e.g., autonomy) might end up as a highly complex and richly nuanced principle with built-in exceptions (p.16).

Arras continues, "The more specified versions of the original principle are different norms from their original source, but they remain tethered to it by advancing the same value in ways that might be action-guiding in particular circumstances" (ibid). He provides the following example to further illustrate his point:

> Schematically, the final action-guiding principle would look something like: Women and men have a decisive right of reproductive liberty except when conditions X, Y, or Z obtain, where good reasons might be given within the ambit of the overarching principle for the enumerated exception clauses (ibid).

In clinical research, the abstract principle of respect for autonomy generates the concrete requirement for researchers to obtain informed consent from prospective research participants. When a conflict arises in a particular case, the act of specification adds exception conditions to the requirement to obtain informed consent, which generates a new requirement that still follows from respect for autonomy.

How are exception conditions generated and how do we ensure these conditions are justified and sufficient? Proponents of specified principlism insist that a robust justification can be achieved through reflective equilibrium. Reflective equilibrium, originally posited and developed by John Rawls (1971), is the endpoint of the process of examining "our moral judgments about a particular issue by looking for their coherence with our beliefs about similar cases and our beliefs about a broader range of moral and factual issues" (Daniels, 2016). To resolve a conflict between cases and moral intuitions, the process to achieve reflective equilibrium involves an examination of our moral intuitions and a further specification of the ethical principles that generate the conflict.

We can examine our moral intuitions and generate exception conditions to informed consent by exploring the strongest cases for proceeding with research without consent. Bearing in mind the history of the development of the waiver of consent, let us examine retrospective review of medical records. In these studies, existing identifiable patient data from electronic databases, medical charts, or other sources of routinely collected data (e.g., results of lab tests, health provider notes, reports) are used to answer one or more research questions. These studies often involve the review of hundreds of records. Some of these records may belong to patients who cannot be contacted, such as deceased patients or patients whose contact information has changed. The time and expense associated with hiring additional research personnel to find and contact hundreds of patients to obtain their consent would be prohibitive, and, as Robert Levine (1986) argues, would not further "the goal of showing respect for the patients whose records we examine" (p.147). Thus, one exception criterion to obtaining informed consent from research participants is when the research would not be feasible to conduct with informed consent.[23]

Medical records reviewed in these studies may contain highly personal and sensitive information. Collecting this information for the purposes of research without obtaining the informed consent of patients may seem problematic; as Levine (1986) notes, "breaches in confidentiality can result in serious social injury" (p.147). Yet, if privacy safeguards and assurances of confidentiality are in place (e.g., de-identification of data, only abstracting data required to answer the research question, seeking research ethics committee review), the risk posed to patients by the use of their data is minimal. Thus, a second exception criterion to informed consent is when the risks posed by research participation are no more than minimal.

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[23] It is important to note that the feasibility of obtaining consent does not rest solely on considerations of resources (e.g., time, expense, staff). There may also be logistical or methodological considerations that play a role in determining feasibility. But the key consideration worth emphasizing here is that, even if researchers had infinite resources, obtaining informed consent would not further the goal of promoting or protecting patients' autonomy.

Retrospective reviews of medical records can also generate scientifically and socially valuable knowledge. According to Vassar and Holzmann (2013), the retrospective review is "a popular methodology widely applied in many healthcare-based disciplines… and valuable information may be gathered from study results to direct subsequent prospective studies" (p.2). In other words, these studies, when properly designed and conducted, have some prospect of social value. Conversely, if a research activity has no prospect of generating scientifically or socially valuable information (e.g., due to poor methodological design), then it should not be conducted even if obtaining informed consent was feasible.[24] Thus, a third exception criterion to obtaining informed consent from research participants is when the research can generate scientifically and socially valuable knowledge.

Finally, informed consent is required when there are foreseeable infringements on patients' autonomy interests. This is because, as respect for autonomy dictates, people must be given the opportunity to choose what should happen to them or their personal information. But patients are neither intervened upon nor approached for additional data collection during a retrospective review of medical records. While there are no bodily infringements that occur in these studies, the use of patient data without their informed consent is an infringement on patient autonomy. However, these infringements are minor when safeguards are in place to protect patients' privacy and confidentiality. Major autonomy infringements include those against bodily integrity (e.g., administering physical examinations, drugs, vaccines) and the use of sensitive heath data (e.g., substance abuse, suicide attempts, criminal activity) without informed consent. Thus, a fourth exception criterion to obtaining informed consent from research participants is when there is no more than a minor infringement on autonomy.

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[24] This is often referred to as the scientific validity requirement of research. According to Ariella Binik and Spencer Hey (2019), "validity imposes an absolute requirement on ethical research… if a study does not support valid inferences, it is unethical" (p.3). They continue by claiming that the scientific and social value requirement "presupposed scientific validity but adds further stipulation that the hypothesis should be relevant to pressing scientific, clinical or social uncertainties" (ibid).

In sum, through the process of specification using the case example of retrospective review of medical records, we arrive at the following action-guiding principle: respect for autonomy dictates a requirement for researchers to obtain informed consent from research participants, except when the research (1) would not be feasible to conduct with informed consent; (2) poses no more than minimal risk; (3) can generate scientifically and socially valuable knowledge; and (4) poses no more than a minor autonomy infringement.

However, we have not yet reached a reflective equilibrium. Reflective equilibrium requires this action-guiding principle to be consistent with our beliefs about other cases, so let us examine the most contemporary case for which the use of a waiver of consent is believed to be justified: a public health cluster-randomized trial evaluating a cluster-level intervention.

Consider the Community Intervention Trial for Smoking Cessation study (COMMIT, 1995). This public health study aimed to evaluate a multi-modal, community-level smoking cessation intervention designed to increase quit rates among cigarette smokers in 22 communities in Canada and the United States. In this cluster-randomized trial, two communities were selected from each of the participating 11 regions (states or provinces) and, within each region, one community was randomly allocated to the control intervention (i.e., continue with usual public health programs for smoking cessation), while the other community was allocated to the experimental study intervention. The study intervention was a mass education program involving (i) public education through media and billboard campaigns (ii) targeted messaging towards smokers from health care providers, and (iii) additional financial resources. Telephone interviews were conducted using random-digit-dialing with cross-sectional samples of approximately 3,000 households per community. Through the telephone interviews, approximately 1,100 smokers were identified in each community to be contacted annually for 5-years with follow-up interviews. Informed consent for the study interventions was not obtained from research participants, but those contacted by telephone or by mail for data collection at baseline and during follow-up could decline to respond. There was no significant impact

on smoking prevalence and no effect on the quit rate of heavy smokes, although there was an improved quit rate for mild to moderate smokers.

In this example, the question is whether the use of a waiver of consent is justifiable for the study interventions, as informed consent would be required during the telephone interviews for data collection. With respect to the study interventions, requiring informed consent would have rendered the trial infeasible. The study interventions in the COMMIT trial were cluster-level interventions targeted at entire communities, e.g., promoting smoke-free policies over the radio, television, and billboards. If we consider research participants to be only those people living within the participating communities who encounter the interventions (rather than people passing through), identifying those who in fact encounter the interventions would not be possible. If we consider all those living in the participating communities to be research participants, requiring the informed consent of hundreds of thousands of individuals would be prohibitively time consuming and expensive. Most importantly, cluster-level interventions often manipulate the physical or social environment in a cluster, making it practically impossible for cluster members to avoid. The unavoidability of cluster-level interventions renders the participant's refusal of consent meaningless, because the decision to decline the intervention cannot be respected.

The public health interventions in the COMMIT trial also posed no more than minimal risk. Recall that minimal risk refers to the incremental physical, psychological, social, and economic risks posed by participation, study interventions and data collection. Given that the control communities were randomized to continue with their usual public health initiatives, there was no incremental risk posed by the control arm. The incremental risk posed by the intervention arm to the other half of the communities was also minimal. For example, there could have been an economic burden placed on communities required to implement various components of the intervention; however, each intervention community was provided with an average of $220,000 per year for four years to support the execution of the intervention.

The COMMIT trial could also produce scientifically and socially valuable knowledge. The value of any study must be determined prior to enrolment and, hence, prior to granting a waiver of consent. A research ethics committee must determine whether the study is likely to produce high-quality scientific evidence that addresses an important health issue. According to the Government of Canada (2021), "Smoking is the most important cause of premature death in Canada. […] About 17% of deaths were due to smoking… [and it] is responsible for more deaths than overweight and obesity, physical inactivity, or high blood pressure. Since the COMMIT trial was a well-designed research study that aimed to increase smoking cessation, there was substantial prospect of scientific and social value. Even though the experimental study intervention did not change quit rates of heavy smokers, the results contributed to a growing body of evidence and were consistent with the findings of many other community studies on smoking cessation.

Finally, the COMMIT trial posed no more than a minor autonomy infringement on community members. Due to the nature of the study intervention, even if cost and time were not an obstacle, obtaining informed consent would not further the goal of showing respect for autonomy. People do not have a choice about what public health interventions are in place in their communities. For example, it is not within the scope of one's autonomy to choose what commercials can be permitted on television or the radio, or what sort of materials can be distributed at community events.

The use of a waiver of consent in the COMMIT trial is justified as it meets the four exception criteria to informed consent. Therefore, the action-guiding principle is consistent with our beliefs about two distinct cases that the waiver of consent was developed to permit. A final step to reflective equilibrium requires an examination of the criteria with our "beliefs about a broader range of moral and factual issues" (Daniels, 2016). Compare these four exception criteria with current CIOMS (2016) international ethical guidelines. A waiver of consent can be granted by a research ethics committee if researchers prove that:

> (1) the research would not be feasible or practicable to carry out without the waiver or modification; (2) the research has important social value; and (3) the research poses no more than minimal risk to participants (p.37).

The first criterion of a waiver of consent confirms that there is indeed a conflict between beneficence and respect for autonomy. If it is feasible to conduct research with informed consent, then there is no conflict between beneficence and respect for autonomy and, therefore, informed consent must be obtained. The second criterion is a requirement of beneficence, and "refers to the importance of the information that a study is likely to produce" (CIOMS, 2016, p.1). Beneficence also requires that risks are minimized in relation to the knowledge to be gained. Hence, the third criterion also stems from a welfare concern: if the research poses no more than minimal risk, then the infringement on patient autonomy through the use of a waiver of consent is justified.

Note that the CIOMS guidelines only invoke welfare criteria for a waiver of consent. There is no criterion stipulating that the research can pose no more than a minor autonomy infringement, and the lack of an autonomy criterion is consistent across ethics guidelines and regulatory documents. Thus, to achieve a reflective equilibrium, we must consider whether the addition of an autonomy criterion better explains our moral intuitions about cases for which the use of a waiver of consent is justifiable. I contend that it does.

First, the autonomy criterion remains consistent with the history of the development of the waiver of consent. For the two types of research studies examined above—retrospective review of medical records and the COMMIT trial—the addition of an autonomy criterion does not affect the broad use of a waiver of consent. In a retrospective review of medical records with privacy and confidentiality safeguards in place, there are only minor autonomy interests at stake and, hence, these studies remain a strong candidate for a waiver of consent. In the COMMIT study, the interventions, like all cluster-level interventions, are not divisible to individual participants. The infringement on the autonomy of individuals living within enrolled communities is minor insofar as there is no infringement on bodily integrity and privacy interests.

Second, the addition of an autonomy criterion better explains cases in which research poses no (or low) risk but the use of a waiver of consent is intuitively problematic. In other words, people have an interest in choosing whether to be enrolled in a study that involves an infringement on their autonomy even if there are no foreseeable infringements on their welfare. For example, people have a choice whether to participate in an innocuous survey study because of their interest in choosing how to spend their time or with whom to share their data. It seems wrong to use a waiver of consent when there is a foreseeable infringement on autonomy, even if there are no foreseeable risks involved in the research.

Finally, the autonomy criterion was generated by the specified principlism framework. This framework is more robust than the rights-based and presumed consent frameworks insofar as it does not fall prey to the criticisms raised against them. Gelinas and colleagues (2016), in support of the rights-based framework, construed autonomy rights too narrowly by excluding patients' right to privacy. Autonomy infringements, according to the specified principlism view, are broadly understood to incorporate bodily integrity and privacy rights. Gelinas and colleagues also failed to explain how rights trade-off against the imperative to conduct socially valuable clinical research. The specified principlism framework, however, explains how principles and their requirements trade-off against one another. Using reflective equilibrium, this framework derives exception criteria to establish the necessary conditions under which the requirement to respect patient autonomy via informed consent can be overridden by the requirements of beneficence.

For the presumed consent framework, Baker and Merz (2018) correctly described the exception to informed consent requirements for emergency research and how the legal doctrine of privilege acts as its foundation. But they failed to appreciate that privilege cannot be invoked in non-emergency settings (i.e., privilege does not provide a reason why informed consent need not be obtained for a retrospective review of medical records). The specified principlism framework, however, is consistent with the history of the waiver of consent, as it grounds the use of a waiver of consent for retrospective reviews of medical records, low-risk social science studies, and public health studies that

evaluate cluster-level interventions. The specified principlism framework also avoids the inconsistencies generated by incorporating trust and transparency into the principle of respect for autonomy.

Now that the specified principlism framework has grounded the use of a waiver of consent, we can consider the implications for pragmatic cluster-randomized trials of *individual-level therapeutic interventions*, such as the MyTEMP trial. Should a waiver of consent have been granted for this study? Only if the four exception conditions are satisfied: the research (1) would not be feasible to conduct with informed consent; (2) poses no more than minimal risk; (3) can generate scientifically and socially valuable knowledge; and (4) poses no more than a minor autonomy infringement.

As has been previously argued, the MyTEMP trial can generate scientifically and socially valuable knowledge. Chronic renal disease is a worldwide public health problem. One of the most common causes of mortality is cardiovascular complications, and many current drugs used to treat cardiovascular disease do not work for this patient population. Reducing the dialysate temperature seems to be one of the most effective and inexpensive interventions to manage cardiovascular complications (Sakkas et al., 20117). However, the MyTEMP trial fails to meet the other three criteria required to justify the use of a waiver of consent.

First, the research would, theoretically, be feasible to conduct with informed consent. Hiring additional research personnel at each of the 84 participating hemodialysis would likely be a cost constraint, but the hemodialysis setting is unique in that health care providers are available and regularly interact with patients. In Canada, patients require in-centre hemodialysis treatments on average for three to four hours a session, three to four times a week. Since the intervention requires health care providers to interact with a patient's dialysis machine, a health care provider could feasibly obtain the patient's informed consent without incurring substantial costs in terms of time and resources.

Second, the risks of the study may seem minimal. According to Sakkas and colleagues (2017), "patients tolerate long term cold dialysis very well, reporting high levels of satisfaction (76%-80%)" while the most commonly reported side effect of

receiving cold dialysis are related to cold sensations and incidences of shivering. But, from the patient's perspective, some people experience cold as deeply unpleasant. Even if for most patients the sensation of cold is tolerable, we need to consider the trajectory of a patient who currently receives treatment at body temperature and already experiences unpleasant coldness whose facility gets randomized to temperature-reduced dialysis. In fact, patients are told to bring jackets, hats, gloves, thick socks, and other warm clothing to their treatments, even in the summer. To be cold to the point of shivering for several hours a day, multiple days per week could threaten a patient's adherence to their treatment. The risks of failing to adhere to treatment or stopping treatment altogether is death, which is more than minimal.

Finally, hemodialysis is an invasive and demanding medical treatment. Patients are required to adhere to strict diets. They are advised to increase protein intake and limit the amount of potassium, phosphorus, sodium, and fluid in their diet, and are given regular tests to ensure they are meeting dietary goals. As a result, some patients are acutely attuned to what goes into their bodies. When a patient's hemodialysis treatment is modified for the purposes of research without their consent, this amounts to bodily intrusion—a major infringement of patients' autonomy. This is because the MyTEMP study changes the way in which hemodialysis is administered for the purposes of research. It is within the scope of a patient's autonomy to choose whether their treatment, which directly enters their body, can be modified for the purposes of research.

Therefore, according to the specified principlism framework, the use of a waiver of consent is not justified in the MyTEMP trial. Indeed, the approach to use a waiver of consent in pragmatic cluster-randomized trials of individual-level therapeutic intervention in the hemodialysis setting will not be justifiable in most cases. This is because of the level of the study interventions. Individual-level interventions are, by definition, directly delivered to individual participants. Because patients regularly interact with health care providers, it is theoretically feasible to obtain their consent. Nevertheless, if informed consent would render the research infeasible, studies evaluating individual-level interventions will often involve infringements on patients' interests in bodily integrity or health information privacy. So even if we assume the research is infeasible to conduct

with consent, poses no more than minimal risk, and can generate valuable knowledge, failing to seek and obtain informed consent for individual-level interventions will often constitute a major autonomy infringement. Thus, the approach to use a waiver of consent for pragmatic cluster-randomized trials of individual-level therapeutic interventions will not be justifiable in most cases. I leave it open that there may be some cases that meet all four criteria and, consequently, the use of a waiver would be morally permissible.

3.4 Conclusion

This chapter began with a brief history of the development of the waiver of consent. The waiver of consent was created to permit the conduct of retrospective reviews of medical records, low-risk research in the social sciences, and public health cluster-randomized trials evaluating cluster-level interventions. Given that the waiver of consent was not developed with pragmatic cluster-randomized trials in mind, an explication of the underlying philosophical framework was required to know when, if ever, a waiver of consent can be used to facilitate the conduct of these trials. I argued that there were several problems with the two frameworks posited in the literature to date. I subsequently posited and defended the specified principlism framework as the most promising foundation for justifying the use of a waiver of consent. According to the specified principlism framework, respect for autonomy dictates that informed consent is required except when the research: would not be feasible to conduct with informed consent; poses no more than minimal risk; can generate scientifically and socially valuable knowledge; and poses no more than a minor autonomy infringement. In most cases of pragmatic cluster-randomized trials that evaluate individual-level interventions, there will be major infringements on patient autonomy. As a result, the approach to use a waiver of consent fails to resolve the conflict between the requirement to respect patient autonomy and the social imperative to conduct pragmatic cluster-randomized trials.

How, then, can socially valuable clinical research proceed if encumbered by the requirement to obtain informed consent? In the next chapter, I explore a third and final approach: the use of alternative models of consent as a means of promoting and protecting patient autonomy while simultaneously facilitating the conduct of pragmatic cluster-randomized trials.

Chapter 4: Alternative models of consent in pragmatic cluster-randomized trials

This thesis aims to address the tension in pragmatic cluster-randomized trials between the requirement to respect patient autonomy and the imperative to conduct socially valuable clinical research. As was established in chapter 1, pragmatic trials are designed to evaluate the effectiveness of an intervention in real-world settings to generate evidence that is directly applicable to the decisions of patients, health providers, and health system managers. Trialists are increasingly using cluster-randomized designs because they are believed to be inherently more pragmatic. By including whole clusters without soliciting informed consent from prospective research participants, cluster randomization can enhance both internal and external validity and ensure that intervention delivery within the trial deviates as little as possible from routine care. But including all-comers without their consent is clearly an infringement of their autonomy. How ought this conflict be resolved?

Those who took the first approach, discussed in chapter 2, attempted to resolve the conflict by arguing that there is an enforceable duty to participate in clinical research. Those who took the second approach, discussed in chapter 3, attempted to resolve the conflict by arguing that a waiver of consent could be broadly used to facilitate the conduct of pragmatic cluster-randomized trials. It is noteworthy that both approaches attempted to resolve the tension between the requirement to respect patient autonomy and the imperative to conduct socially valuable clinical research by eliminating the need for informed consent. In fact, the literature is almost exclusively concerned with the question: when, if ever, should socially valuable clinical research proceed without informed consent? I believe this has created a false dichotomy: the idea that either written informed consent is obtained or not neglects to take account of the diversity of methods that can be used to obtaining informed consent, some of which may be ethically justified and practically feasible for pragmatic cluster-randomized trials.

In this chapter, I proffer and defend a third and final approach to address the tension in pragmatic cluster-randomized trials. My approach is to investigate how the ends of autonomy and pragmatism can be served simultaneously. Specifically, my

solution to the overarching thesis question requires an answer to the focal question of this chapter: can alternative models of consent promote and protect the autonomy of patients and facilitate the conduct of pragmatic cluster-randomized trials?

To answer this question requires an investigation into how informed consent is meant to respect the autonomy of research participants. In section 4.1, I explicate the theory that informed consent is properly understood as an autonomous authorization. An explication of autonomous authorization provides the conditions that, when met, allows us to determine when an informed consent process achieves its goal of respecting the autonomy of prospective research participants. Using these conditions, in section 4.2, I explore four alternative models of consent—namely, simple opt-out consent, integrated consent, short form consent, and electronic consent—and argue that the latter three models can satisfy the conditions of an autonomous authorization. This means that alternative consent models, when designed and implemented correctly, may be ethically permissible and practically feasible for the broader set of pragmatic cluster-randomized trials. In section 4.3, I address some of the implications of using alternative consent models, and conclude in section 4.4 that this approach, in effect, resolves the tension in pragmatic cluster-randomized trials.

4.1 Informed consent as an autonomous authorization

Recall that the ethical principle of respect for autonomy requires "that individuals [are] treated as autonomous agents" (National Commission, 1978a, p.4). This principle means people should be free to choose and act in ways they see fit, and that we give due regard for their decisions. It is operationalized in clinical research as the researcher's obligation to obtain the informed consent of prospective participants prior to their enrollment in a study.[25] It would seem, then, that a theory of what it means to be an

[25] Some philosophers argue that informed consent is inappropriately grounded in the ethical principle of respect for autonomy. For example, Onora O'Neil (2003) claims that "if informed consent is ethically important, this cannot be because it secures some form of individual autonomy" (p.5). This is because "informed consent procedures protect choices that are timid, conventional, and lacking in individual autonomy (variously conceived) just as much as they protect choices that are self assertive, self knowing, critically reflective, and bursting with individual autonomy (variously conceived)" (p.6). She suggests that "our aim in seeking others' consent should be not to deceive or coerce those on the other end of a

autonomous person is required to know how the informed consent process can act as a means of protecting and promoting patient autonomy.[26]

However, determining whether a person is autonomous does not necessarily guarantee that an informed consent will be provided. According to Ruth Faden and Tom Beauchamp (1986)—who are credited with developing and defending the prevailing theory of informed consent (Miller & Wertheimer, 2010, p.80-81)—the capacity to act autonomously is distinct from acting autonomously. For example, they state that an "autonomous person who signs a consent form without reading or understanding it is *qualified* to give an informed consent, but has failed to do so" (Faden and Beauchamp, 1986, p.237, italics in original). While the capacity to act autonomously is a precondition to providing an informed consent, on their view consents and refusals themselves are properly understood as actions (p.235). Therefore, they posit that the theory underlying informed consent should be a theory of autonomous actions rather than autonomous persons.

Faden and Beauchamp (1986) claim that an informed consent is a particular kind of autonomous action; namely, an autonomous authorization. On their view, informed consent occurs if and only if a patient or prospective research participant "with (1) substantial understanding and (2) in substantial absence of control by others (3)

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transaction or relationship" (ibid). On this view, consent represents a transaction between patient-participants and clinician-researchers, which ultimately is grounded in trust. However, trust-based views of informed consent (see O'Neil, 2002) have been criticized when they are proposed as a comprehensive theory of consent. Critics claim that intervening on patient-participants without their informed consent primarily wrongs the individual, not future individuals due to a decline in public trust (Eyal, 2014). Moreover, failing to obtain informed consent is problematic even in cases when the public could never find out about such violations (ibid).

[26] Some philosophers have taken this approach to developing a theory of informed consent. For example, Benjamin Freedman (1975) argues that informed consent is a voluntary choice made by a responsible (i.e., competent, autonomous) person. Freedman posits that a responsible person makes choices "on the basis of reasons, arguments, and beliefs…, remains open to the claims of reasons… [and] is capable of living with his life-plan; he can live with the consequences of his choices" (p.35). Thus, on this view, if we can determine that a person is responsible, we demonstrate respect for their autonomy by accepting their choices.

intentionally (4) authorizes a professional [to intervene]" (p.278). These are the four conditions of an autonomous authorization, explicated as follows.

4.1.1 Substantial understanding

Faden and Beauchamp (1986) claim that we need an account of understanding that can identify the conditions under which a person understands the nature and the foreseeable implications of their actions (p.251). They state,

> The typical pattern of understanding in informed consent settings is for patients or subjects to come *to understand that* they must consent to or refuse a particular proposal by *understanding what* is communicated in an informational exchange with a professional (p.250, italics in original).

In other words, to have substantial understanding of an action, a person must (1) understand that they are providing an authorization and (2) understand what they are authorizing (p.300-304).

The first condition of substantial understanding is derived from an analytical claim: a person cannot provide an autonomous authorization without providing an authorization; thus, a person cannot understand that they have provided an informed consent without understanding that their act of consent is an act of authorization. (Faden and Beauchamp, 1986, p.301). For a person to understand that their act is an authorization, a person "must understand, at a minimum, that by consenting, X has given a specific agent, Y, express permission to do something," (ibid) and that their express permission is required for Y to do it. This is what Faden and Beauchamp call the "permission-giving and transfer-of-control function of authorization" (p.279-280).

The second condition of substantial understanding—to understand what one is authorizing—does not require professionals to disclose a long list of items. Although the literature on informed consent has focused on the question of what professionals should be obligated to disclose to patients and prospective participants when soliciting consent, Faden and Beauchamp (1986) remodel the problem as follows: "If patients and subjects are ignorant or inexperienced, what can professionals do to facilitate obtaining informed

consents based on substantial understanding?" (p.305). They claim that "effective communication is *without peer as the most important form of understanding*" (p.255, italics in original).

Effective communication requires ample opportunity for discussion between prospective participants and professionals. Patients and prospective participants must be able to understand what the professional is saying when she is disclosing information and when she is responding to their questions, while the professional must be able to understand what is said to them in order to provide satisfactory answers to questions (Faden and Beauchamp, 1986, p.314). The central idea is that the role of the professional seeking informed consent is to teach—to explain clearly what is expected of the patient or prospective participant and what should be expected of the professional. This involves the use of illustrations, examples, words of encouragement, and attention to non-verbal behaviour (e.g., body posture, unhurried, courteous, sufficient privacy) (p. 315).

Professionals soliciting consent for research will need to disclose information about the study during the informed consent process to initiate the discussion. Faden and Beauchamp suggest that only a "core disclosure" is needed to help prospective participants achieve substantial understanding. This core disclosure, on their view, should be guided by three considerations: professionals must disclose (1) the facts that prospective participants subjectively consider to be important in deciding when to participate; (2) the facts that the professional believes to be important for the decision; and (3) the purpose of seeking consent, including "the nature and implications of consent as an act of authorization" (Faden and Beauchamp, 1986, p.308).

The disclosure of this information should serve to initiate effective communication, as the satisfaction of substantial understanding need not occur during a single encounter (Faden and Beauchamp, 1986, p.315-316). In fact, Faden and Beauchamp claim that an iterative feedback strategy is "simultaneously the best method available for assessing understanding in the context of interpersonal communication and achieving it" (p.328). Their recommended feedback loop strategy is to have prospective participants restate, in their own words, what has been disclosed to them. In this way

prospective participants and professionals can be assured that they have reached a shared understanding about what is being authorized.[27]

4.1.2 Substantial noncontrol

The second condition of an autonomous authorization is substantial noncontrol.[28] Faden and Beauchamp's (1986) use of noncontrol expresses the negative right to not be controlled—the right that others refrain from controlling one's actions or choices—measurable by the basic concepts of influence and resistance to influence (p.256). Some actions are wholly noncontrolled, such as those that have not been the target of an influence attempt or have been the target of an unsuccessful influence attempt. Other actions are controlled to a greater or lesser degree depending on how they are influenced. They claim that there is a continuum from completely controlling influences to completely noncontrolling influences. On one extreme is coercion, which occurs when acts are "entirely dominated by the will of another" (p.258). Coercive interventions "always entirely compromise autonomy by wholly controlling action" (p. 259) because, on their view, coercion occurs when one person intends to influence another person by presenting a severe, credible, and irresistible threat (p.339). The coerced person's choice is wholly controlled; it is not their own, "but effectively that of the other" (p.339).

On the other extreme of the influence continuum is persuasion, defined as an influence attempt that does "not deprive the actor of any way of willing what he or she

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[27] To be clear, the prospective participant and health professional need not have an identical understanding about what is being authorized (Faden and Beauchamp, 1986, p.310). Due to the specialized and technical nature of many procedures, it cannot be expected of prospective participants to have the same level of understanding as the health professional. But a prospective participant and health professional "must at least share an understanding that is sufficiently broad and objective" (ibid). The approach to achieve shared understanding "recognizes that an informed consent includes many of the features of a valid contract, chief of which is that the parties agree to the essential features of the arrangement" (ibid). Thus, in the context of clinical research, both parties should share an understanding that an authorization for research participation is needed and should share an understanding of the essential features of what will be authorized.

[28] The concept of noncontrol is synonymous with a narrow understanding of voluntariness, defined as freedom from controlling conditions. According to Faden and Beauchamp (1986), and later reiterated by Beauchamp and Childress (2019), the concept of voluntariness is often analyzed "in terms of the presence of adequate knowledge, the absence of psychological compulsion, and the absence of external constraints" (p.136). Such a broad definition leads to equating voluntariness with autonomy, and thus—to avoid confusion—the concept of noncontrol is used as a condition of autonomous action.

wishes to do or believe" (Faden and Beauchamp, 1986, p.258). Persuasion is the "intentional and successful attempt to induce a person, through appeals to reason, to freely accept—as his or her own—the beliefs, attitudes, values, intentions, or actions advocated by the persuader" (p.339). Persuasion attempts can be resisted, but once a persuasive argument is accepted, the persuaded person "willingly acts or accepts a belief as one's own" (p.259) and, consequently, is uncontrolled.

On the continuum between completely noncontrolling and completely controlling influences is deception, indoctrination, seduction, and incentivization, which are subsumed under the generic term "manipulation" (Faden and Beauchamp, 1986, p.259, p.355-373). Manipulations can be as controlling as coercion or as noncontrolling as persuasion (p.259), but all manipulative influences attempt to sway an individual to do what the manipulator requests. The most common form of manipulation in the health care context is informational manipulation, defined as a deliberate act of managing information that changes a person's understanding of a situation and motivates them to do what the manipulator requests (Beauchamp and Childress, 2019, p.136).

Many types of informational manipulation, including lying and withholding information, compromise autonomous choice to a greater or lesser degree. The way information is disclosed, including tone of voice, body language, and framing information positively or negatively, can also manipulate an individual's choice. Faden and Beauchamp (1986) claim that the threshold of a substantial noncontrolling influence varies depending on the context and thus is difficult to establish (p.362), and "whether a particular influence is compatible with substantial noncontrol will not be obvious and will require experienced judgment and extensive knowledge of the situation and the person giving consent" (p.373). Thus, they recommend that those seeking consent avoid, to the greatest degree possible, all forms of manipulation. But they place no restrictions on the use of persuasion because, on their view, it "is an acceptable form of influence in informed consent contexts" (ibid).

4.1.3 Intentional action

The third condition of an autonomous authorization is that it is an intentional action. Faden and Beauchamp (1986) claim that acts are either intentional or not (p.248). For an action to be intentional, the action must be "willed in accordance with a plan" (p.245); otherwise, if there was no plan involved, the action would be accidental. The term "willed" rather than "wanted" or "desired" is used to capture the breadth of intentional actions. Actions can be intrinsically or instrumentally wanted, but they may also be merely tolerated (p.245-246). It is common in health care settings that the act of consenting is an intentional act of toleration; for instance, a person may not want a scar on their face but nonetheless intentionally agrees to surgery to remove cancer that results in a scar on their face (p.247). Whether or not an action is wanted or merely tolerated, Faden and Beauchamp's straightforward heuristic for determining whether an action is intentional is for the actor, upon reflection, to be able to say, "I did as I planned" (p.243).

4.1.4 Authorization

The three criteria outlined above are the sufficient conditions of an autonomous action. But what distinguishes informed consent as a particular kind of autonomous action that is restricted to the medical and research contexts is the fourth and final criterion—authorization. According to Faden and Beauchamp (1986), when a person authorizes a professional to intervene, the person "both assumes responsibility for what one has authorized and transfers to another one's authority to implement it" (p.280). The authorization is what permits the professional to do something that is mentioned or detailed in the consent agreement. Without an authorization to intervene, there cannot be in any meaningful sense an informed consent.

4.1.5 Effective consent

In sum, Faden and Beauchamp (1986) argue that informed consent is properly understood as an autonomous authorization, which is provided when a patient or prospective research participant with substantial understanding and in substantial absence of control intentionally authorizes a professional to intervene. However, Faden and Beauchamp distinguish autonomous authorization from what they call effective consent.

Effective consent is analyzable in terms of "the web of cultural and policy rules and requirements of consent that collectively form the social practice of informed consent in institutional contexts where groups of patients and subjects must be treated in accordance with rules, policies, and standard practices" (p.277). In other words, it is a policy-oriented, legal, or institutional sense of informed consent (p.280). It is effective when "it has been obtained through procedures that satisfy the rules and requirements defining a specific institutional practice in health care or in research" (ibid).

Informed consent in policy contexts often rely on its interpretation as an autonomous authorization (Faden and Beauchamp, 1986, p.284).[29] Although the conditions of an autonomous authorization are not "logically necessary" conditions for an effective consent,[30] Faden and Beauchamp take it as "morally axiomatic that they ought

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[29] Consider Canada's regulatory requirements for informed consent. According to these research regulations, consent must be "free, informed, and ongoing" (CIHR et al., 2018). Article 3.1 to 3.3 address each of these conditions respectively. Article 3.1 states that "consent shall be given voluntarily" because individuals have a right to choose "to participate in research according to their own values, preferences and wishes" (ibid). To ensure consent is voluntary, researchers and research ethics committees must "be cognizant of situations where undue influence [i.e., manipulation], coercion or the offer of incentives may undermine the voluntariness of a participant's consent to participate in research" (ibid). It also states that "coercion is the most extreme form of undue influence [and] would negate the voluntariness of a decision to participate," and that undue influence, manipulation, and incentives "at the extreme" can undermine voluntariness (ibid). This aligns with Faden and Beauchamp's explication of the condition of noncontrol—so long as there exists substantial noncontrol, consent is freely given. Article 3.2 requires researchers to "provide to prospective participants, or authorized third parties, full disclosure of all information necessary for making an informed decision to participate in a research project" (ibid). The regulations do not specify what information is necessary; rather, it provides a list of items to disclose that are "generally required for informed consent" (ibid). In fact, it states that "not all the listed elements are required for all research," and "additional information may be required in particular types of research or under particular circumstances" (ibid). This reflects Faden and Beauchamp's depiction of the core disclosure process used to achieve substantial understanding: the nature and implications of agreeing to participate should be made clear, but many of the other elements depend on what patients and professionals believe to be important for the decision. Article 3.2 also states that "the key to informed consent is that prospective participants understand the information being conveyed to them by researchers" and that they "be given adequate time and opportunity to assimilate the information provided, pose any questions they may have, and discuss and consider whether they will participate" (ibid). This reflects Faden and Beauchamp's claim that the best way to achieve substantial understanding is effective communication. Article 3.3 states that "consent shall be maintained throughout the research project" (ibid), which means that participants' consent is revocable and, consequently, researchers have an "ongoing duty to provide participants with all information relevant to their ongoing consent to participate in the research" (ibid). Clearly, regulatory consent requirements rely on consent interpreted as an autonomous authorization.

[30] Tom Beauchamp, in his later work with James Childress (2019), claim that "health care professionals cannot reasonably be expected in all circumstances to obtain a consent that satisfies the conditions of highly demanding autonomy-protective rules" (p.121). They maintain that "autonomous choice—following the first sense of 'informed consent'—ought to serve as the benchmark for the moral adequacy of

to serve… as the benchmark or model against which the moral adequacy of [effective consent] is to be evaluated" (ibid). Since the goal of an informed consent process is to facilitate autonomous decision-making by enabling prospective participants to decide whether to participate in clinical research, the informed consent process should conform to the conditions of an autonomous authorization. In other words, any informed consent process used to recruit patients into research should be conducted with the intention to maximize the likelihood that the conditions of an autonomous authorization can be satisfied to protect and promote the autonomy of research participants.

4.2 Alternative models of consent

The conventional written informed consent process used in clinical research, as described in the introductory chapter of this thesis, often involves an initial determination of eligibility by one's health provider and, if determined eligible by a member of the research team, an invitation to participate. The invitation to participate typically consists of a conversation with a third-party recruiter who, often using a lengthy form as a guide, provides a full disclosure of all the elements of informed consent required by regulations. The recruiter then answers questions to promote comprehension and gives the prospective research participant ample time to read the form and voluntarily sign it. Since the conventional written informed consent process poses methodological, logistical, and financial barriers to the conduct of pragmatic trials, several alternative models of consent have been proposed (McKinney et al., 2015; Kalkman et al., 2017).

In our review of the reporting of informed consent in 1,988 pragmatic trials published between 2014 and 2019, we identified the use of four alternative models of consent: simple opt-out consent; integrated consent; short form consent; and electronic consent (Zhang et al., 2021). According to Kalkman and colleagues (2017), "all these

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institutional rules of consent," but recommend evaluating "institutional rules in terms of both respect for autonomy and the probable consequences of imposing burdensome requirements on institutions and professionals" (ibid).

alternatives 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" (p.184). Indeed, alternative models of consent are more friendly to the pragmatic aims of trials than the conventional written informed consent process because they aim to cause minimal deviations from clinical practice and achieve higher enrollment of heterogenous populations.

But can alternative models of consent protect and promote the autonomy of prospective research participants? An explication of autonomous authorization in the previous section provided the conditions that, when met, allow us to determine when an informed consent process can achieve its goal of protecting and promoting the autonomy of research participants. In what follows, I examine whether the four alternative models of consent that have been used to facilitate the conduct of pragmatic cluster-randomized trials can conform to the conditions of an autonomous authorization.

4.2.1 Simple opt-out consent

Simple opt-out consent is a process wherein potential research participants are included in research unless they decline verbally or in writing. This consent model often accompanies broadcast notification. Broadcast notification is the use of general notifications, such as posters placed in prominent locations within clinics, that inform patients of ongoing research. Broadcast notification may also include specific notification to affected patients by, for example, distributing pamphlets or letters.

Faden, Beauchamp, and Kass (2014) posit that broadcast notification with an opt-out mechanism (i.e., simple opt-out) can be used in pragmatic trials. They ask us to consider "a pragmatic, randomized clinical trial that compares two widely used hypertension medications" (p.767). Key features of their hypothetical example that, on their view, would make it "ethically acceptable for the study to proceed… without specific notification to affected patients" include the following features: (1) the "clinician's judgement is respected" by allowing her to make the final enrollment decision and to deviate from the protocol for any patient at any time; (2) the study is "unlikely to negatively affect expected clinical outcomes for patients;" (3) the

interventions "are similar in administration and side-effect profiles…, have acceptable side-effect profiles, and adverse events are rare;" and (4) it is "unlikely that patients would have personal preferences for one drug over the other" (ibid). When these four features are present in a pragmatic trial, Faden and colleagues suggest that "simply telling patients about the study through a streamlined process and giving them an opportunity to decline participation would be an ethically acceptable, warranted mechanism of authorization. It may even be acceptable… [for] the study to proceed with broad notification to the community of the system, without requiring that individual patients be told about the randomization" (ibid).

Simple opt-out consent has been used to facilitate the conduct of pragmatic cluster-randomized trials in the hemodialysis setting. Consider the MyTEMP trial (Textbox 1) in which patients at participating dialysis centres were provided a two-page letter describing the study, including their centre's allocated temperature protocol and the right for patients to opt out (Al-Jaishi et al., 2020b). Although each centre ultimately decided how to distribute the information sheets, the researchers suggested that the two-page letters be provided by an administrative assistant to patients when they register for their dialysis session, or by a nurse while patients are dialyzing. Posters were also placed in highly accessible areas[31] at participating centres to notify patients of the ongoing trial (see Figure 1 and 2). Patients could opt out of their centre's allocated treatment protocol, but since patient data and outcomes were obtained from centralized administrative data sources there were no data collection procedures from which to opt out.

Although used to facilitate the conduct of the MyTEMP trial, does the use of simple opt-out consent allow patients to autonomously authorize their participation in research? According to McKinney and colleagues (2015), this consent model "honors individual decisional rights to some extent but does not provide an individualized approach to disclosure of information and consent" (p.498). Neither Faden and colleagues nor McKinney and colleagues provide an argument with respect to how

[31] For example, posters were placed in waiting areas and near scales where all patients are weighed before treatment.

patients' autonomy is honoured. While practically appealing, does simple opt-out consent plausibly satisfy the conditions of an autonomous authorization?

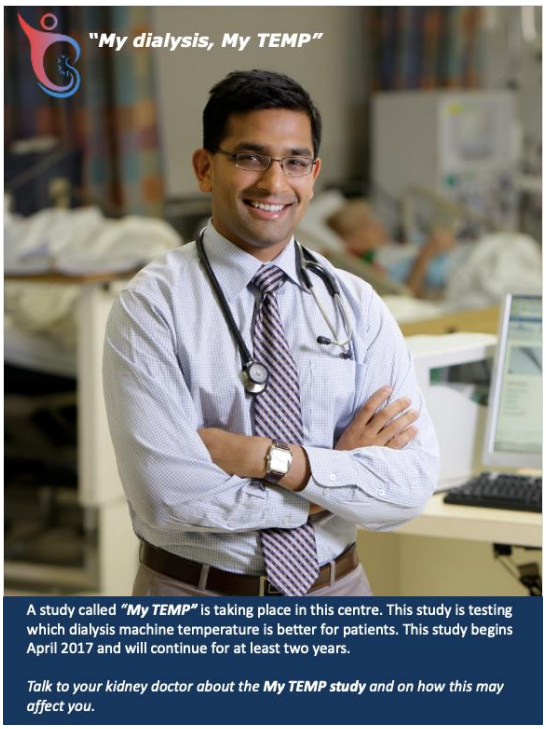

Figure 1: Poster placed in control arm facilities in the MyTEMP trial.

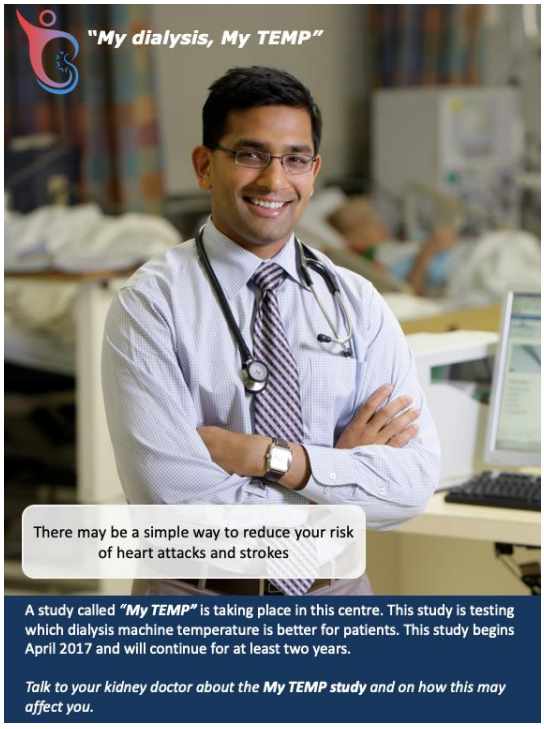

Figure 2: Poster placed in intervention arm facilities in the MyTEMP trial.

I maintain that simple opt-out consent does not meet the requirements of an autonomous authorization and, thus, does not respect the autonomy of research participants. This consent model does not allow a patient to intentionally authorize their participation and a failure to opt out does not constitute an intentional authorization. The argument is simple: a person authorizes a professional to intervene when she "assumes responsibility for what one has authorized and transfers to another one's authority to implement it," (Faden and Beauchamp, 1986, p.280) and, for this authorization to be intentional, she should be able to say upon reflection, "I did as I planned." Since the default option on this consent model is participation, if a study proceeds with only general notification to the community—for example, if posters are the only means of communicating information with patients—then there is no assurance that people will be

aware of their ability to decline participation. Indeed, the MyTEMP trial poster does not indicate that patients can opt out; it only states that patients can talk to their kidney doctor about how the trial may affect them. Evidently patients cannot provide an intentional authorization if they are unaware of their option to opt out.

The distribution of written information alongside the use of posters may help to mitigate the concern that patients are not intentionally authorizing their participation. Consider Ben Saunders (2012) defense of simple opt-out consent schemes for organ procurement. Saunders argues that an opt-out mechanism should be considered a form of implied (sometimes called tacit) consent. Implied consent occurs when "the patient's actions [or inaction] indicate that they consent, although no express signal is given" (p.70). An example, according to Saunders, is when the chairperson of a meeting declares that a motion will be carried if no one voices an objection. For silence to be considered an informed consent, Saunders claims that "it must be clearly communicated to all involved that this is how their silence will be interpreted. Moreover, it must be possible for people to opt out without facing unreasonable costs for doing so" (p.71). Similarly, if a simple opt-out consent process includes written information provided to patients that clearly communicates how patients can opt out of a study without facing unreasonable repercussions, then—according to this argument—patients' intentional silence should be construed as an intentional, albeit implicit, authorization.

But for simple opt-out consent to conform to an autonomous authorization, it must also be the case that all patients have substantial understanding that neglecting to consult one of their health providers to opt out of the study constitutes their authorization. Patients with end-stage renal disease have higher prevalence rates of cognitive impairment and dementia than the general population (Kuo et al., 2019), with some studies suggesting that 19% to 28% of patients beginning dialysis between 66-80 years of age are diagnosed with dementia (Citroner, 2018) and the prevalence of cognitive impairment is as high as 87% (Murray et al., 2006). Most patients treated with hemodialysis have difficulty thinking clearly, concentrating, expressing themselves, and remembering information; this is often described as the feeling of being in a "dialysis fog," or having "brain fog" or "kidney brain" during treatment (Home Dialysis Central,

2021). Simply distributing an information letter to this patient population provides no assurance that all or even most patients will have read the information sheet, let alone understand that their silence constitutes an informed consent.

Moreover, simple opt-out consent does not require any communication between prospective participants and health providers to enroll patients into a study. It requires patients to initiate discussion to refuse participation. But the physician-patient relationship has long been recognized as a fiduciary relationship because of the power differential between patients and health providers. Patients may be too intimidated to approach their physician to initiate discussion, particularly when posters show that the physician is also involved as a researcher in the trial. Other factors that can inhibit patients receiving hemodialysis from seeking information from their physicians include the fear of displeasing those who provide life-sustaining treatment or of appearing to waste the physician's time. Since communication between health providers and patients is central to the facilitation of substantial understanding, patients may not adequately understand what they are authorizing without some mechanism in place to ensure patients can read and understand the information that has been provided to them.

Therefore, simple opt-out consent cannot conform to the conditions of an autonomous authorization. Patients who remain unaware of their ability to opt-out can neither provide an intentional authorization, nor have substantial understanding that neglecting to opt-out constitutes an authorization to be involved in research. Hence, this consent model should not be permitted unless a waiver of consent is granted by a research ethics committee. According to the Tri-Council Policy Statement 2, one of the criteria for a waiver of consent is a "plan to provide debriefing… that may also offer participants the possibility of refusing consent and/or withdrawing data" (CIHR et al., 2018). The use of broadcast notification with an opt-out mechanism is best understood as an instance where waiver of consent is approved with a strategy for debriefing or notifying patients of ongoing research that provides patients the opportunity to refuse the intervention, the use of their data in research, or both. But, as was argued in the previous chapter, a waiver of consent will not be permissible for most pragmatic cluster-randomized trials in the hemodialysis setting.

4.2.2 Integrated consent

Kim and Miller (2014) propose an "integrated consent model" for pragmatic trials that evaluate treatments used routinely in clinical practice "that have been validated through well-controlled clinical trials" (p.770). The integrated consent model uses consent procedures in clinical practice as a standard for obtaining informed consent in clinical research:

> When prescribing a treatment, physicians discuss its rationale, any alternatives, and their likely consequences (including both potential benefits and likely side effects) and obtain the patient's agreement. In most cases, no written consent or form is necessary, and often only a brief discussion is needed (p.770).

Analogously, when a health provider seeks to enroll a patient into a pragmatic trial, the integrated consent model requires them to discuss pertinent information about the research before obtaining the patient's verbal consent. The information discussed includes the purpose of research, research procedures (e.g., randomization), potential benefits, risks, and alternative options. The disclosure of information would also follow a script approved by a research ethics committee. If the patient decides to participate, the health provider "does what she would ordinarily do in the course of her practice—that is, document the clinical interaction. She would record the fact that the consent conversation took place…that there was agreement, and that a treatment (A or B) was chosen—including the process of random selection. She would also check a box [in their health record] so that the patient's outcomes are sent to the trial database" (ibid).

Kim and Miller's clinical-style consent model is an important advance in informed consent for pragmatic trials. It has been used to facilitate recruitment in pragmatic trials, but to date it has not been used in pragmatic cluster-randomized trials in the hemodialysis setting. If it were used in the MyTEMP trial, clinical staff at participating centres would discuss pertinent information about the trial before documenting their verbal consent or refusal in the patient's health record (see Textbox 3 for a potential script for this conversation).

Textbox 3: Example script for integrated consent.

As we've discussed, your kidneys are not functioning, and you require hemodialysis to sustain your life. Hemodialysis is not a cure for kidney failure; it cleans your blood by pumping it through a device that will remove waste and excess fluids.

We've also discussed the many risks and side effects associated with hemodialysis. If you recall, heart disease is the most common cause of death among patients receiving hemodialysis. This is because the treatments used to effectively prevent heart disease in the general population (such as statins and anti-platelet drugs) are largely ineffective in patients on hemodialysis.

In some small studies, researchers found that using a cooler dialysate temperature compared to a standard dialysate temperature was associated with a lower rate of death from heart disease. But we honestly do not know if a cooler temperature is better than the standard temperature.

Our centre has agreed to participate in a clinical trial, called the MyTEMP trial, to examine the effects of cooler dialysate temperature compared to the standard dialysate temperature. Eighty-four hemodialysis centres in Ontario have been randomized (like a flip of a coin, so that we can obtain scientifically useful results) to provide either temperature-reduced hemodialysis or the standard temperature from April 2017 until March 2021.

If you agree to participate in this research study, you will receive hemodialysis at the temperature our centre has been told to provide to patients. This may be the standard temperature you would normally receive, or it may be the colder temperature. There are no special procedures or visits required to participate. You may, however, experience additional coldness. I recommend wearing additional layers or bringing extra blankets to your dialysis session.

Taking part in this study is voluntary. You have the option to not participate at all or you may choose to leave the study at any time (called withdrawal). If you choose to withdraw from the study, you should inform me or another member of the clinical staff. Whatever you choose, it will not affect the usual medical care that you receive, and your agreement to participate in the study does not relieve the researchers or our centre from our legal and professional responsibilities. If at any point you or I think it would be good to change the dialysate temperature, we can do that.

If you agree to participate, I will document our discussion and your decision on the electronic health record system under a secure research page. You will not be paid for taking part in this study and there will be no costs associated with participation.

Do you have any questions? [Answer any questions they may have.] May I have your verbal consent for participation in this study?

However, there are two reasons why the integrated consent model might be problematic for pragmatic cluster-randomized trials in the hemodialysis setting. First, Kim and Miller (2014) stipulate that integrated consent is only applicable to pragmatic trials that seek to evaluate treatments validated through previously conducted trials. But routine hemodialysis care lacks a strong evidence base; in fact, nephrology has the fewest clinical trials of any medical discipline, and many of the trials that have been conducted suffer from poor design and reporting (Strippoli, Craig, & Schena, 2004). Since Kim and

Miller require the study interventions to be validated through well-controlled clinical trials, it seems that pragmatic trials evaluating many hemodialysis interventions may not proceed with integrated consent.

I contend that Kim and Miller's argument is too limiting. They posit that the interventions need to be validated through previously conducted clinical trials, but do not explain why they limit the scope of the integrated consent model in this way. One plausible explanation is that integrated consent was developed to facilitate the conduct of certain types of pragmatic trials, namely those that compare "two commonly prescribed medications for an outpatient condition such as hypertension, [where] the only material departure from clinical practice may be replacing the physician selection of treatment with a randomized selection" (p.769). It could be, then, that the emphasis on the need for validation from previously conducted clinical trials is to ensure that the only material departure from clinical practice is randomization. In fact, they state that integrated consent is permissible when "all the patient's welfare interests are in line with what he would receive in ordinary clinical care and the only unusual element—that of randomization—is integrated into the clinical consent conversation" (p771). This means that when interventions have been previously validated, or when the study interventions are unlikely to adversely impact patients' medical interests, it is permissible to use integrated consent. Some treatments used routinely in hemodialysis care have not been previously validated by clinical trials,[32] but nonetheless are unlikely to adversely affect patient interests because there is sufficient evidence to suggest parity with competent care. Thus, Kim and Miller would likely agree that integrated consent can be used in pragmatic cluster-randomized trials evaluating hemodialysis interventions if the interventions have been previously validated or are unlikely to adversely impact patients' medical interests.

Second, Kim and Miller (2014) claim that the integrated consent model can only be used for pragmatic trials that meet the necessary regulatory criteria for a waiver or

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[32] Some treatments used routinely in hemodialysis care are only supported by evidence generated from non-randomized trials, such as observational studies, or physiological evidence.

alteration of consent. This is because “the proposed model does not include all the elements of informed consent required by… federal regulations (e.g., it lacks explicit statement regarding voluntariness and confidentiality, because the context renders them unnecessary” (p.771). This does not have to be the case—all required elements of informed consent can be verbally disclosed. But whether a pragmatic trial meets the regulatory criteria for a waiver or alteration of consent need not be the determining factor of whether the integrated consent model can be used. Instead, we ought to consider whether integrated consent can conform to the conditions of an autonomous authorization.

The integrated consent model undoubtedly allows prospective participants the opportunity to provide an intentional authorization. In other words, this model is designed to allow prospective participants to decide in favour of or against participating in research. The question is whether prospective participant can satisfy the condition of substantial understanding and substantial noncontrol. I believe that both the condition of substantial understanding and substantial noncontrol can be satisfied by using an integrated consent model.

Recall that the condition of substantial understanding is achieved primarily through effective communication, used to assist patients in making an informed choice about whether to participate in research. The integrated consent model aims to do just that: a health provider has a clinical-style conversation with a patient wherein they discuss pertinent information about the research in reasonably nontechnical language, and the health provider answer all the patient’s questions. Recent empirical evidence suggests that one-on-one discussions with prospective research participants is one of the most effective ways to improve their understanding (compared to written information, test and feedback quizzes, multimedia presentations, and other miscellaneous methods) (Nishimura et al., 2013; Dellson et al., 2018; Houghton et al., 2020).

It is important that the information disclosed in the integrated consent process includes the purpose, nature, and implications of consent, and the facts that both patients and professionals believe to be important when deciding whether to participate. While the

disclosure of information listed by Kim and Miller (2014)—i.e., the purpose of research, randomization, potential benefits, risks, and alternative options—are facts commonly considered to be important, it is not always sufficient for a patient to have substantial understanding. According to Kim and Miller, the only difference between clinical practice and a pragmatic trial comparing interventions used routinely in clinical practice is the use of randomization. But this is not always true. Pragmatic trials are diverse. Some may include nontherapeutic interventions or have additional data collection procedures. Thus, patients should be aware of how participation in a trial will alter the trajectory of the care they would otherwise receive. Allowing patients to ask questions also provides an opportunity to ensure that the facts they believe to be important are disclosed.

The condition of substantial noncontrol can also be satisfied by using integrated consent, but not the integrated consent model proposed by Kim and Miller (2014). They state that their consent model does not include all the elements of informed consent; specifically, "it lacks explicit statements regarding voluntariness and confidentiality, because the context renders them unnecessary" (p.771). Faden and Beauchamp (1986) recommend that those seeking consent avoid, to the greatest degree possible, all forms of manipulation including the withholding of information (p.363). Withholding information can compromise autonomous choice and, in this case, refraining from disclosing the voluntary nature of the choice (i.e., to refuse participation entirely or withdraw from the study at any time) risks undermining the prospective participant's autonomy. If the reason of withholding the voluntary nature of participation is the concern that too many people will refuse participation, health professionals soliciting consent can use persuasion "to induce a person, through appeals to reason, to freely accept—as his or her own—the beliefs, attitudes, values, intentions, or actions advocated by the persuader" (p.339). In other words, those soliciting consent can explain the voluntary nature of participating while simultaneously encouraging participation.[33]

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[33] An additional concern about control may be the power dynamic between health professionals and patients. For example, patients on hemodialysis may fear that their care will be compromised if they refuse to participate in a study conducted by their nephrologist. To address this concern, it is vital to stress the voluntary nature of participation, which can be supplemented with a statement that any choice made will not relieve researchers or clinical staff from their legal and professional responsibilities (see Textbox 3).

In sum, the integrated consent model proposed by Kim and Miller, with minor modifications, can conform to the conditions of an autonomous authorization. Integrated consent in its simplest form is a clinical-style consent process wherein a patient's verbal consent is documented in their medical record. If recruiters effectively communicate the nature of the research, the implications of authorizing participation, and the facts that patients and professionals deem to be important with adequate protections against coercion and manipulation, a verbal disclosure without written documentation[34] gives prospective participants the opportunity to provide an autonomous authorization.

4.2.3 Short form consent

Short form consent refers to a process involving a simplified or condensed consent form, often one or two pages, that is reviewed verbally with a prospective research participant (McKinney et al., 2015). The form must contain all regulatory elements of informed consent and be signed by the research participant. A written summary of what will be disclosed verbally to the prospective participants must be approved by a research ethics committee. If the prospective participant provides their written consent, a copy of the summary and the short form are provided to them.

Short form consent is akin to integrated consent. It is a clinical-style consent process wherein recruiters have a discussion with prospective participants about the nature of the research, the implications of authorizing participation, and other important facts about the trial. Prospective research participants can ask questions, and a brief consent form (one or two pages) containing this information is provided to them. A notable difference between short form consent and integrated consent is that a prospective participant's written signature on the brief form is required. Given the similarities between these two consent models, short form consent can meet the conditions of an autonomous authorization. With adequate protections against coercion and manipulation, a verbal disclosure with written documentation gives prospective participants the opportunity to provide an autonomous authorization.

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[34] Some research regulations, such as those in the United States (DHHS, 2018), require researchers to justify a waiver of documentation in cases where consent is not signed by the research participants.

4.2.4 Electronic consent

The term "electronic consent" (also called e-consent) encompasses a wide variety of consent process (CT:IQ, 2019).[35] It is often broadly defined as "the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive websites, biological recognition devices, and card readers, to convey information related to the study and to obtain and document informed consent" (DHHS, 2016). For the purpose of this discussion, electronic consent is limited to an in-centre consent process[36] that involves clinical or research staff members providing prospective research participants with an electronic device (e.g., desktop or laptop computers, mobile phones, tablets) to access information about the trial and to obtain an electronic signature on a digital form. Patients should have an opportunity to contact members of the study team to ask questions prior to and after providing their electronic signature, and they should be able to revisit the digital form using secure login details.

This consent model will be used to facilitate the conduct of the HiLo trial, a pragmatic cluster-randomized trial in the hemodialysis setting (Edmonston et al., 2021). This trial explores whether "strict phosphate control improves, worsens, or has no effect on clinical outcomes," specifically all-cause mortality and all-cause hospitalization. They plan to randomize 80 to 120 U.S. hemodialysis centres managed by DaVita Inc and the University of Utah to either a higher (>6.5 mg/dl) or a lower (<5.5 mg/dl, current standard of care) serum phosphate target protocol. The interventions, which consist of phosphate binder prescriptions and dietary recommendations, will be implemented by local dieticians. They expect to enroll 4,400 adults with kidney failure undergoing three-times-weekly in-centre hemodialysis using electronic consent. Patients will be provided

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[35] Electronic consent often refers to one of four different processes: (1) digital consent form with hand-signed consent; (2) digital consent form on an approved device with electronic signature; (3) digital consent form using cloud-based or online software with electronic signature; or (4) digital consent form using biometric consent (i.e., consent is documented using fingerprint identification or face recognition technology).

[36] Electronic consent can also refer to an "at-home" or remote process. This model is similar to the standard informed consent process, except the consultation and discussion occurs through an online medium (e.g., Skype, Zoom, WebEx) and the patient's consent is provided verbally or via an electronic form.

with tablets that connect to secure web-based videos. Three concise videos, currently available on the study's website (https://www.hilostudy.org), provide information on "clinical research participation, phosphate and its management in kidney failure, and the 'nuts and bolts' of HiLo," co-narrated by a nephrologist and a patient with kidney failure (ibid). A central team of nephrologist will be available to answer questions by telephone. The HiLo trial was approved centrally by the Duke University research ethics committee.

Some empirical evidence suggests that patients prefer electronic consent to receiving written information (Karunaratne et al., 2010; Zeps, Northcott, & Weekes, 2020). Other potential benefits of electronic consent include: the ability to use certain technological functions (e.g., text-to-speech software, translation software) to enroll patients commonly excluded from research (e.g., visually impaired, non-English language speakers); lower burden on site staff as they only facilitate the consent process; and improved monitoring and management of consents, refusals, and withdrawals (TransCelerate Biopharma Inc., 2017). These benefits are all important in pragmatic trials, which aim to include all-comers—especially those who have previously been excluded from research—with fewer or no additional research staff or resources.

But there are also substantial barriers to the use of electronic consent (TransCelerate Biopharma Inc., 2017; Chen et al., 2020). Regulatory barriers include longer research ethics committee approval times due to inexperience with or reluctance to use technology, and some countries or institutions may not legally accept electronic signatures. Logistic and financial barriers include the need for backup systems, longer setup time and higher initial costs and resources than paper forms, and technical limitations (e.g., the need to use certain software or devices). Additional concerns have been raised about the willingness and ability of older adults to use technology to provide consent, although recent findings from a mixed-methods study found that an electronic consent process "is feasible to implement with older adults and acceptable to this

population, but… efforts to optimize design of [electronic] consent forms for older adults are warranted" (Jayasinghe et al., 2019, p.124).[37]

When the barriers to electronic consent are addressed, this consent model can facilitate the conduct of pragmatic trials, as demonstrated by the HiLo trial. But can this consent model conform to the conditions of an autonomous authorization? Like short form consent and integrated consent, electronic consent allows prospective participants to intentionally decide in favour of or against participating in research. The condition of substantial noncontrol is likely to be met, particularly if those who create the digital media are attentive to how the information is presented. Once again, the question is whether prospective research participants can satisfy the conditions of substantial understanding with this consent model.

Unlike short form consent and integrated consent, electronic consent does not necessitate patient-provider interactions nor discussions to occur. Consider the HiLo trial. Prospective research participants are provided with information about the trial through various forms of digital media (text, graphics, and videos) and only if they have questions will they reach out to a team of nephrologists to discuss the information. One potential problem is whether substantial understanding can be achieved without a conversation occurring between prospective participants and health professionals to ensure that there is a shared understanding of what has been disclosed.

Faden and Beauchamp's (1986) theory of informed consent is silent on the question of how health professionals and prospective participants should come to an agreement about participation. Recruiters often use one-on-one discussions to effectively communicate information because it is "frequently the most available and critical means to the end of understanding" (p.314). But one-on-one discussions are not a necessary

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[37] The first part of this study involved focus groups to gather feedback from older adults (age 65 years or older) about the advantages and disadvantages of a multimedia, interactive tablet-based consent process compared to paper-based consent. The second part involved randomizing older adults to view either a tablet-based consent or paper-based consent for a mock clinical trial. While "user-friendliness, immediate comprehension, and retention of the tablet-based consent were similar to the paper-based consent" (Jayasinghe et al., 2019, p.124), concerns about using a tablet-based consent process centered on the need among older individuals for orientation to using the tablet itself.

condition of an autonomous authorization, nor is it the only means to the end of understanding (ibid). Growing evidence suggests that the use of interactive, multimedia technology can improve patients' comprehension and retention of key elements of informed consent (Karunaratne et al., 2010; Friedlander et al., 2011; Rowbotham et al., 2013; Rothwell et al., 2014; Jayasinghe et al., 2019; Zeps, Northcott, & Weekes, 2020). Successful teaching also takes time, hence why Faden and Beauchamp claim that there is nothing about informed consent that "demands that its conditions be satisfied in a single sitting or setting" (p.315). Electronic consent provides patients the opportunity to review information at any time and, like the HiLo trial's website, it can contain additional information to address common misunderstandings (e.g., the purpose of research). Although one-on-one discussions are not necessary, it is prudent to have staff available for one-on-one discussions if feasible. Staff should be trained or previously skilled in communicating study-specific information to be responsive to the needs and concerns of patients considering participation.

4.3 Implications of using alternative models of consent

Integrated consent, short form consent, and electronic consent can conform to the conditions of an autonomous authorization. While these three consent models use different media to relay information about the trial and to document the prospective participant's choice, each requires a person to intentionally authorize their participation in research; otherwise, the patient is not included in the research study. These models differ from simple opt-out consent, which does not seek an authorization but rather presumes it. There is also nothing inherent in the design and implementation of integrated consent, short form consent, or electronic consent that inhibits the researchers' ability to effectively communicate with prospective research participants to help them achieve substantial understanding in the absence of control by others.

These alternative models of consent can also be consistent with the aims of pragmatism. Trials are seldom purely pragmatic or purely explanatory, but various design choices make a trial more or less pragmatic (Loudon et al., 2013). Pragmatic trials are designed to mirror real-world settings; thus, a very pragmatic trial will include all or most patients who would receive the interventions in clinical practice, recruit patients at the

time of clinical presentation, minimally disrupt the workflow of participating clinics, and be resource efficient (i.e., not require specialized training or additional staff). Whether integrated consent, short form consent, or electronic consent is used, the consent process can mirror procedures used for clinical consent and achieve high rates of recruitment.[38] This means that when the research setting is a primary care setting without research staff, research ethics committees ought to allow researchers flexibility in using verbal, written, or electronic disclosure processes, provided they are otherwise consistent with regulatory disclosure requirements.

There are also clear advantages of using integrated consent, short form consent, or electronic consent over the conventional written informed consent process in pragmatic cluster-randomized trials. On the one hand, the written informed consent process often involves dedicated study coordinators or research staff to solicit, obtain, and record consent. Consent forms are criticized for being lengthy, overly complicated, and can take up to an hour to read. On the other hand, clinical style consent models, such as integrated consent, short form consent, and electronic consent, are more cost-effective and practical. These alternative consent models do not require specialized research staff; they are simply integrated into the clinical consent process. Forms are clear and succinct or there are no forms at all, and it takes less time to converse with one's health provider about the research study than to read a lengthy form and then ask questions. While it is widely expected that there are advantages in terms of costs and feasibility, empirical studies may be needed to substantiate these claims.

However, researchers and research ethics committees may not be considering alternative models of consent. In our review of the reporting of informed consent in 1,988 pragmatic trials published between 2014 and 2019, only 53 trials (2.9%) reported the use

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[38] High rates of recruitment have been achieved using integrated consent. For example, the Rethinking Clinical Trials (REaCT) program uses integrated consent in their pragmatic oncology trials that compare different approved cancer treatment strategies. Enrollment in traditional cancer trials is dismal; less than 5% of patients approached provide consent. But enrollment in REaCT trials are "well over 80% of those approached," and estimates suggest that "the integrated [consent] model allows a five-fold reduction in costs, due to the ease of data collection and management, and to the efficiency of enrollment" (Ansari & Petch, 2018).

of alternative consent models (Zhang et al., 2021). In most cases (1,683 trials; 85%) standard written informed consent was reported, which to some degree undermines that concern that written informed consent inhibits the conduct of pragmatic trials.[39] It is also noteworthy that 139 trials (7.5%) reported no consent or a waiver of consent, and that "trials that self-identified as pragmatic had a higher prevalence of not obtaining consent than those that did not use this label" (ibid). These results demonstrate that researchers and research ethics committees, when confronted with designing and reviewing a pragmatic trial, will in most cases choose or approve written informed consent or no consent. This is the false dichotomy to which I alluded at the outset of this chapter. The choice should not be between the conventional written informed consent process and no consent. In the same vein, the best approach to answering the overarching thesis question—of how we can address the tension in pragmatic cluster-randomized trials between the requirement to respect the autonomy of prospective participants and the imperative to conduct socially valuable research—is not to find ways to eliminate the need for informed consent. What I have argued in this chapter is that the use of alternative consent models can be consistent with the aims of pragmatism and the requirement to protect and promote patient autonomy.

In fact, our recent interview and focus group study involving patients and families with experience of hemodialysis found that "patient partners supported [consent] approaches that allow patients to make an individual decision regarding trial participation" (Nicholls et al., 2021, p.13). Participants stressed the importance of having a choice regarding trial participation and "were significantly more willing to participate in trials that employed a choice-based approach compared to trials that did not" (p.12). While participants were indifferent about the specific process for enabling their choice, they preferred active notification (e.g., information sheets) over passive notification (e.g.,

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[39] It is also important to note that only 688 of 1,988 trials (34.6%) in the review were cluster randomized, and that cluster randomization was significantly associated with not obtaining informed consent. Although there was a high prevalence (85%) of reporting written informed consent in all 1,988 pragmatic trials, there was poor reporting of justifications for not obtaining consent and, when justifications were provided, these were not always in line with the minimum criteria stated in international ethics guidelines for research involving humans.

posters) (p.12). These findings are consistent with studies conducted by Courtright and colleagues (2017) and Weinfurt and colleagues (2017).

Although alternative models of consent can be consistent with the aims of pragmatism, there are certain implications for their use in cluster-randomized trials. As described at the outset of this chapter, cluster randomization is an attractive design for embedding pragmatic trials into the hemodialysis setting. But clusters are often randomized before it is possible to identify and recruit research participants. According to the *Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials*, if informed consent cannot be obtained from participants before cluster randomization, it should be sought as soon as possible after randomization and before the implementation of any study interventions or data collection (Weijer et al., 2012).

When informed consent is sought after randomization, in either a cluster-randomized trial or a patient-randomized trial, this can be a source of selection bias (particularly, identification and recruitment bias). Identification bias occurs when "the assignment that was not properly randomized or the randomized assignment was not sufficiently concealed, and so the person enrolling participants was aware of allocation sequence and influenced which patients were assigned to each group based on their prognostic factors" (Mansournia et al., 2017). Recruitment bias occurs when "an investigator is aware of the random sequence and decides to enroll patients with certain prognostic factors only if they are known to be assigned to a particular treatment strategy" (ibid). In other words, when participants are enrolled by someone who is aware of their cluster's allocated intervention, or when participants provide consent based on the knowledge of their cluster's allocated intervention, this could induce differential recruitment—either different numbers of patients included in the study arms, or differences in the baseline characteristics of patients between the study arms (Higgins & Green, 2008; Giraudeau & Ravaud, 2009; Easter et al., 2021, Eldridge et al., 2021). Identification and recruitment bias may undermine the trial's internal validity and the researchers' ability to detect any possible effects of the interventions, meaning that the trial would not yield any scientifically useful information.

The concern that informed consent may be a source of bias is commonly raised as a justification for not obtaining informed consent in a cluster-randomized trial. When everyone is included in research, there is no need to identify or recruit patients; consequently, there is no potential for identification and recruitment bias. But the potential for identification and recruitment bias in and of itself does not justify dispensing with consent. Rather, it may necessitate changes to the informed consent process that can prevent or mitigate potential selection biases (Eldridge, Kerry, & Torgerson, 2009; Weijer & Taljaard, 2019).

To prevent selection bias, researchers should, when possible, identify and recruit patients before clusters are randomized. Again, identification and recruitment bias can both be prevented if the recruiters are not aware of what intervention will be allocated to the participant, and if patients are not aware of which intervention they will receive if they decide to participate. This will prevent recruiters enrolling patients based on certain prognostic factors (e.g., a recruiter may decide only to enroll frail patients if they will be in the intervention arm rather than the control arm) and prevent patients from deciding to participate based on what they will receive.

If it is not possible to identify and recruit before randomization, blinded recruiters or clinical staff trained on the importance of blinded recruitment should be used. Blinded recruiters will be unaware of their cluster's allocated intervention, whereas clinical staff may be aware of the allocation but will refrain from informing patients about the allocation to keep prospective participants blinded to avoid differential recruitment. While this may lessen the pragmatic nature of a trial (because of the need to hire additional research staff or train clinical staff to recruit patients), a less-than-ideal pragmatic trial design may be necessary to mitigate the risk of bias that, if present, could completely undermine the scientific validity of the study.

It is essential that participants, to the degree possible, remain blinded to the study interventions. Researchers may be tempted to provide different information based on the intervention to which the cluster has been allocated, but "whatever the timing of recruitment, both intervention and control groups should be given similar information

about the trial before consent" (Eldridge, Kerry, & Torgerson, 2009). This means that participants can be fully informed about the details of the trial while concealing their cluster's allocation status.

In most cases, the informed consent process will require a full disclosure of important facts about the trial. But in some cases, participants may be able to determine their allocation when the intervention is administered over time, which can lead to performance bias or attrition. Performance bias occurs when there are systematic differences in the care delivered or in patient behaviours between the study arms (other than those differences due to the intervention under investigation). For example, if health providers are aware of their cluster's allocation, they might modify the type of care delivered to certain patients; or informing patients in the control arm about the intervention could cause them to seek out the active intervention.

If there is a demonstrably high risk of performance bias due to an inability to maintain blinding, an alteration of consent may be required. The onus falls on researchers to demonstrate that a full disclosure of required elements (e.g., the study objective, hypothesis, and interventions) is incompatible with the scientific ends of the study, and that research participation poses only minimal risk. In the altered consent process, prospective participants "must be told they are participating in a trial and that information is being withheld from [them] to protect the scientific validity of the study," and after the study is complete, "participants should be informed of the details of the trial, the intervention to which they were allocated, and the results of the study" (Weijer & Taljaard, 2019).

Only when a clear justification is provided that neither informed consent nor an alteration of consent is feasible (and participation poses only minimal risk) may researchers and research ethics committee consider simple opt-out consent or a waiver of consent. In no case should a waiver of consent be approved for a drug or vaccine intervention, as this would permit a standard of consent for research that is below that of clinical practice.

4.4 Conclusion

This chapter began with an explication of informed consent as an autonomous authorization. Informed consent is provided when a prospective research participant, with substantial understanding and in substantial absence of control by others, intentionally authorizes a health professional to intervene. Given that the conditions of an autonomous authorization are the benchmark against which the moral adequacy of effective consent is to be evaluated, I examined four alternative models of consent that have been used in pragmatic trials. I argued that simple opt-out consent could not conform to the conditions of an autonomous authorization, and that it is properly conceived of as a waiver of consent. I subsequently argued that integrated consent, short form consent, and electronic consent can conform to the conditions of an autonomous authorization. As a result, the use of alternative consent models can resolve the conflict between the requirement to respect patient autonomy and the imperative to generate socially valuable knowledge through the conduct of pragmatic cluster-randomized trials.

Chapter 5: Conclusion

The last two decades have seen an almost exponential increase in the number of pragmatic trials. This is in part due to their potential to generate socially valuable knowledge. However, existing ethics guidelines and regulatory frameworks were developed for explanatory trials and are thus difficult to apply to pragmatic trials. The lack of specific guidance for pragmatic trials has led to inadequate protections for research participants in some cases (Horn et al., 2018; Goldstein et al., 2018a) and unnecessary obstacles to socially valuable research in others (Roberts et al., 2020; Almufleh & Joseph, 2021). As a member of an international, multidisciplinary team, I helped identify ethical issues raised by pragmatic trials generally (Goldstein et al., 2018b; Nicholls et al., 2019; Nicholls et al., 2021a) and pragmatic cluster-randomized trials in hemodialysis settings (Goldstein et al., 2019; Al-Jaishi et al., 2020a; Nicholls et al., 2020; Nicholls et al., 2021b).

This thesis focused on resolving one crucial issue posed by pragmatic cluster-randomized trials in hemodialysis settings, which is the tension between the requirement to respect patient autonomy and the imperative to conduct socially valuable clinical research. In chapter 1, I described the tension in detail. Briefly, informed consent requirements are deeply rooted in ethics, human rights law, and regulations. However, informed consent requirements can pose substantial methodological, logistical, and financial challenges that can undermine the aims of pragmatic trials to mirror real-world clinical settings and to include all patients who would receive the treatments under investigation as a part of their routine clinical care. Moreover, trialists are increasingly using cluster-randomized designs to further the ends of pragmatism because they are believed to be inherently more pragmatic than patient-randomized designs. By randomizing whole clusters (e.g., hemodialysis centres) without soliciting informed consent from individual patients within, cluster randomization can achieve both internal and external validity and ensure that intervention delivery within the trial deviates as little as possible from routine care. But including all-comers without their informed consent is clearly an infringement of their autonomy. The overarching question, then, is whether the

infringement on patient autonomy is adequately justified by the imperative to conduct socially valuable research.

To provide an answer for this question, I focus on the following sub-questions in chapters 2 through 4 respectively: Do patients have an enforceable moral duty to participate in pragmatic cluster-randomized trials without their informed consent? Should a waiver of consent be broadly used to facilitate the conduct of pragmatic cluster-randomized trials? Can alternative models of consent promote and protect the autonomy of patients and facilitate the conduct of pragmatic cluster-randomized trials? Each of these sub-questions represents a different approach to answering the overarching thesis question. In what follows, I summarize the main arguments of each approach, describe how each question above is ultimately answered, and explain how the answers to the sub-questions constitute a solution to the overarching thesis question. Next, given the focus on pragmatic cluster-randomized trials in hemodialysis settings, I clarify which of my arguments generalize beyond the hemodialysis setting to other clinical contexts. I conclude by raising two questions left unanswered in this thesis to be addressed in future work.

5.1 Summary of approach 1: enforceable moral duty

To resolve the tension between the requirement to respect patient autonomy and the imperative to conduct socially valuable research, I critically analyze the argument that patients have a moral duty to participate in low-risk clinical research that offers the prospect of direct therapeutic benefit. Although there has been considerable debate among philosophers as to whether a moral duty to participate in clinical research exists, the arguments articulated in favour of a moral duty only support a *prima facie* duty; a duty that can be overridden by countervailing considerations. If we accept these arguments as sound, then people ought to agree to participate in research unless they have sufficient reasons to decline. However, these arguments, in and of themselves, fail to give an account of how clinical research can proceed without obtaining informed consent from prospective research participants.

What is required to resolve the conflict is a convincing argument that supports an enforceable moral duty—a duty that, by definition, obviates the requirement to obtain informed consent. If such a moral duty exists, it would act as sufficient grounds to override the requirement to obtain the informed consent of prospective research participants, thereby allowing pragmatic cluster-randomized trials to proceed uninhibited. Thus, I construct three of the strongest arguments in defense of an enforceable moral duty grounded in social contract theory, deontological theory, and consequentialist theory respectively.

First, the social contact argument posits that, by tacitly agreeing to live in a society whose government provides publicly accessible health care, citizens incur an enforceable duty to participate in clinical research analogous to our enforceable duty to participate in the judicial system. Philosophers, such as John Harris (2005) and Rosamond Rhodes (2017), argue that enforceability is justified only when the research is socially and scientifically valuable; poses no more than minimal risk; and is in the interest of participants and the public. A compelling case in which this enforceable duty would be justified would be pragmatic cluster-randomized trials in the hemodialysis setting because of the poor prognosis of end-stage kidney disease, the lack of robust evidence for many treatments routinely used in this setting, and patients who participate in these trials may have some prospect of direct therapeutic benefit and are often the ones who will benefit from the completion of the study (since end-stage kidney disease is a chronic condition). Nevertheless, I argue that there are morally relevant differences between the judicial and research contexts that undermine the analogy, and that the implication of accepting their argument results in an unjust or practically unworkable research system.

Second, the deontological argument, proffered by Rhodes (2008), posits that rational agents have a perfect duty of self-preservation and, since participating in clinical research that aims to preserve one's own life or autonomy offers the best chance for achieving the ends of self-preservation, rational agents have a perfect duty to participate in such research. Once again, a compelling case for this enforceable duty would be pragmatic cluster-randomized trials in the hemodialysis setting. Unlike most research

contexts, the benefits gained by the completion of these studies often applies to current and future patients as well as those who participate. Moreover, patients on hemodialysis are at a greater risk of dementia and Alzheimer's disease diagnoses; thus, a person is acting to preserve their autonomy by participating in these trials. But I argued that participating in clinical research does not necessarily offer patients a good chance, let alone the best chance, for preserving one's life or autonomy. Moreover, an enforceable duty to participate in research is antithetical to one of the core tenets of Kantianism as such a duty clearly prohibits people from adopting the ends of research as their own.

Third, I draw upon Peter Singer's (1972) consequentialist argument supporting a moral duty to prevent suffering and death by donating to charity to construct an analogous argument that we have a duty to prevent suffering and death by participating in clinical research, limited only by a sacrifice of something with comparable moral significance. Enrolling patients into a pragmatic cluster-randomized trial in the hemodialysis setting allows them to contribute to knowledge that can reduce suffering and prevent death caused by end-stage renal disease and, when participation in research minimally deviates from the care patients would otherwise receive, there is no sacrifice of comparable moral importance. But I demonstrate that this argument rests on faulty assumptions about the benefits of clinical research. Empirical evidence suggests that an enforceable duty to participate would result in a greater number of individuals being exposed to harms for little or no social benefit. Moreover, the consequentialist argument results in a counter-intuitive conclusion: any research, regardless of the harms posed to participants, can be conducted without consent provided that the research can prevent the suffering and death of more people than those participating in the research.

Since each argument outlined above succumbs to persuasive counterarguments, patients do not have an enforceable moral duty to participate in clinical research. Barring any new and compelling arguments in support of such a duty, informed consent remains an essential protection of patient autonomy and, thus, this approach fails to resolve the tension in pragmatic cluster-randomized trials. The question that remains is when, if ever, is it permissible for pragmatic cluster-randomized trials to proceed without consent?

5.2 Summary of approach 2: waiver of consent

In chapter 3, I examine an approach taken by philosophers and trialists alike who argue that a waiver of consent can be broadly used to facilitate the conduct of pragmatic cluster-randomized trials. But research regulations, including the waiver of consent and its component criteria, were not developed with pragmatic cluster-randomized trials in mind. I provide an overview of the history of the development of the waiver of consent to demonstrate that it was created to permit the conduct of retrospective reviews of medical records with adequate privacy and confidentiality protections and low-risk research in the social sciences. I show that the scope of a waiver of consent expanded to include public health cluster-randomized trials that evaluate cluster-level interventions (i.e., interventions indivisible at the individual level, such as promoting lifestyle changes on local radio), but it is unclear whether its scope should include pragmatic cluster-randomized trials that evaluate individual-level interventions (i.e., interventions directly delivered to individual participants, such as prescribing drugs, physical activity regimens, or hemodialysis treatments to patients).

To know when, if ever, a waiver of consent is justifiable in pragmatic cluster-randomized trials that evaluate individual-level interventions, I explicate two philosophical frameworks that indicate when the use of a waiver of consent is justified. First, the rights-based framework proposed by Gelinas and colleagues (2016) suggests that the use of a waiver of consent is justified when obtaining informed consent is impracticable and either patients' rights are not infringed upon or, if an infringement occurs, the rights infringement is minor and outweighed by the expected social value of research. Based on this framework, the use of a waiver of consent would be justified for many pragmatic cluster-randomized trials in the hemodialysis setting, specifically when they "involve aspects of care over which institutions, not patients, hold a right of control" (p.39). But I argue that this framework construes autonomy-based rights too narrowly, fails to consider that the right to be free of experimentation without consent may be absolute, and—most importantly—neglects to explicate how patients' rights can be overridden by the prospect of generating socially valuable knowledge.

Second, the presumed consent framework suggests that the use of a waiver of consent is justified only when an overwhelming majority of the prospective research participants would agree, if asked. Baker and Merz (2018) ground the use of a waiver of consent in the legal doctrine of privilege, while Kim and Miller (2016) ground it in the ethical principle of respect for autonomy. Based on this framework, the use of a waiver of consent would be rarely (if ever) justified for pragmatic cluster-randomized trials in the hemodialysis setting because empirical evidence suggests that many people do not take part in research when asked. But even if an overwhelming majority of hemodialysis patients would agree to participate in research, I argue that neither privilege nor respect for autonomy can ground a waiver of consent. Although privilege can be invoked as a defense for not obtaining consent in emergency settings, I argue that privilege cannot ground exceptions to consent in non-emergency settings (i.e., the waiver of consent). I also argue that, if a waiver of consent is grounded in respect for autonomy, people would be able to make an autonomous decision without the act of making a choice—a clearly absurd proposition. Without a foundation in ethics or law, the presumed consent framework fails to ground the use of a waiver of consent. But even if a novel foundation could be provided, I argue that the reliance on patient preferences would unduly restrict the use of a waiver of consent from research that it was created to permit.

Given the flaws in both frameworks, I advance a specified principlism framework as a more promising foundation for the waiver of consent. Briefly, the specified principlism framework is used to resolve conflicts between abstract principles by using the method of reflective equilibrium to generate exception conditions to the ethical norms generated by the principles. Thus, the criteria of the waiver of consent are a specification of the exceptional cases in which it is morally permissible for the imperative to conduct socially valuable clinical research to override the requirement to respect patient autonomy. By appealing to cases in which the use of a waiver of consent is uncontroversial, I demonstrate that the use of waiver of consent is justifiable when the research: (1) would not be feasible to conduct with informed consent; (2) poses no more than minimal risk; (3) can generate scientifically and socially valuable knowledge; and (4) poses no more than a minor autonomy infringement. I subsequently demonstrate that the MyTEMP trial would not meet all these criteria.

I conclude that, in most cases of pragmatic cluster-randomized trials that evaluate individual-level interventions, there will be more than a minor autonomy infringement on patient autonomy. This was because studies evaluating individual-level interventions will often involve infringements on bodily integrity or the use of sensitive health information. This means that a waiver of consent should not be broadly used to facilitate the conduct of pragmatic cluster-randomized trials that evaluate individual-level interventions in the hemodialysis setting and, therefore, this approach fails to resolve the tension in pragmatic cluster-randomized trials.

5.3 Summary of approach 3: alternative consent models

Due to the inadequacies of the first two approaches, my strategy for resolving the tension in pragmatic cluster-randomized trials is motivated by the question: can the ends of autonomy and pragmatism be served simultaneously? In chapter 4, I argue that it is possible to facilitate the conduct of pragmatic cluster-randomized trials while protecting and promoting the autonomy of prospective research participants. My solution is to draw a distinction between consent requirements in existing policy and informed consent as an autonomous authorization. An autonomous authorization is provided when prospective research participant with substantial understanding and in substantial absence of control intentionally authorizes a professional to intervene. As the goal of an informed consent process is to facilitate autonomous decision-making, any consent process used in clinical research should be conducted with the intention to maximize the likelihood that the conditions of an autonomous authorization can be satisfied.

Since the conventional written informed consent process poses a barrier to the conduct of pragmatic cluster-randomized trials and because the use of a waiver of consent should rarely be used to facilitate their conduct, I explore four middle-ground alternative models of consent that have been used in pragmatic trials—simple opt-out consent, integrated consent, short form consent, and electronic consent—to see whether they conform to the conditions of an autonomous authorization. Simple opt-out consent refers to a process wherein potential research participants are included in research unless they decline verbally or in writing. While used to facilitate the conduct of the MyTEMP trial, I argue that this alternative consent model does not satisfy the conditions of an

autonomous authorization as a failure to opt out of a study does not constitute an intentional authorization. Moreover, distributing information via posters or letters provides no assurance that all patients, or even most patients, will understand that not opting out constitutes their consent.

Subsequently, I argue that the latter three alternative consent models can satisfy the conditions of an autonomous authorization. Both integrated consent and short form consent are clinical-style consent processes wherein health providers briefly discuss with prospective participants the nature of the research, the implications of authorizing participation, and the important facts about the trial. In integrated consent, consent is provided verbally. In short form consent, consent is documented in writing. Electronic consent makes use of electronic devices and a variety of media to disclose information about the trial, prospective research participants can contact members of the study team to ask questions, and consent is documented in digital form. Each approach uses different media to relay information about the trial and to document the prospective participant's choice, but they all require prospective participants to intentionally authorize their participation and provide ample opportunity for prospective participants to achieve substantial understanding absent control from others.

I maintain that integrated consent, short form consent, and electronic consent can be designed and implemented consistent with the aims of pragmatism. Pragmatic trials aim to recruit all or most patients at the time of their clinical presentation, while minimally disrupting the workflow of participating hemodialysis facilities and being resource efficient. These consent models have all been used to facilitate the conduct of pragmatic trials, are consistent with clinical consent procedures, do not require specialized staff or training, and are likely more cost-efficient and practical than the conventional written informed consent process. This means that clinical-style consent models are ethically permissible and feasible for pragmatic cluster-randomized trials in the hemodialysis settings. In other words, these models can promote and protect the autonomy of patients and facilitate the conduct of pragmatic cluster-randomized trials.

5.4 Generalizability

In sum, this thesis answers the question of how we strike an appropriate balance between the requirement to respect patient autonomy and the imperative to conduct socially valuable pragmatic cluster-randomized trials. My solution to the overarching thesis question is to argue that alternative models of consent can serve the ends of autonomy and pragmatism simultaneously.

While this thesis focused on pragmatic cluster-randomized trials in the hemodialysis setting, many of the arguments within extend straightforwardly to pragmatic cluster-randomized trials in other clinical contexts. With respect to the moral duty to participate in clinical research, the MyTEMP trial (Al-Jaishi et al., 2020b) was used to illustrate the type of clinical research for which patients could plausibly have an enforceable duty to participate. In fact, pragmatic cluster-randomized trials conducted in hemodialysis settings provide a compelling case in which an enforceable duty could be justified based on the social contract, deontological, and consequentialist arguments put forth in chapter 2.

However, the reasons why each of these arguments fails does not depend on features of hemodialysis. The social contract argument fails because the judicial system and research context differ in substantial and meaningful ways that undermine the argument by analogy, and operationalizing the enforceable duty will either disproportionately burden those with illness or result in an inferior recruitment system than the current volunteer-based system. The deontological argument fails because—aside from an enforceable duty being antithetical to one of the core tenets of Kantianism—participating in clinical research, whether it is in the hemodialysis setting or another setting, is not a patient's best chance for preserving their life or autonomy. And the consequentialist argument fails because it rests on the faulty assumption that the more people who participate in research the greater the social benefits, and because it would allow for research participants to be exposed to substantial harm, including death, without their consent. Hence, these arguments generalize beyond the hemodialysis context.

The arguments in chapter 3 also extend straightforwardly to pragmatic cluster-randomized trials in other clinical contexts. The history of the waiver of consent shows that it was developed to facilitate the conduct of retrospective reviews of medical records and low-risk research in the social sciences. Its scope expanded over time but has never included pragmatic cluster-randomized trials that evaluate individual-level interventions in the hemodialysis setting. This does not mean that the scope of the waiver of consent cannot be expanded to include these or other trials. To know when a waiver of consent is justified beyond the scope of what it was developed to permit, the underlying philosophical framework can be used, but its application (i.e., whether the waiver of consent can be broadly used to facilitate a particular type of research) will be context dependent.

The specified principlism framework can be informative for pragmatic cluster-randomized trials that evaluate individual-level interventions across a variety of clinical settings. Recall that, according to this framework, a waiver of consent will be justified for any research study that (1) would not be feasible to conduct with informed consent; (2) poses no more than minimal risk; (3) can generate scientifically and socially valuable knowledge; and (4) poses no more than a minor autonomy infringement. While I argue that the use a waiver of consent cannot be broadly used to facilitate pragmatic cluster-randomized trials in the hemodialysis setting, this was due to the level of the MyTEMP trial's interventions rather than the clinical setting in which it was conducted. As individual-level interventions such as prescribing drugs, administering vaccines, or modifying the temperature of patients' hemodialysis treatments are directly delivered to patients, these will involve more than a minor infringement on patients' autonomy interests if informed consent is not obtained. Thus, pragmatic cluster-randomized trials that evaluate individual-level interventions will often pose more than a minor autonomy infringement irrespective of the clinical context.

Finally, the arguments in chapter 4 generalize beyond the context of hemodialysis settings. In this chapter, pragmatic cluster-randomized trials in the hemodialysis setting were used to illustrate how each consent model has been or could be used to facilitate their conduct. However, the arguments about whether the four alternative models of

consent—simple opt-out consent, integrated consent, short form consent, and electronic consent—can satisfy the conditions of an autonomous authorization did not rely on features of the hemodialysis setting. The reason why simple opt-out consent cannot satisfy the conditions of an autonomous authorization was because it does not permit intentional action. For an action to be intentional, it must be willed in accordance with a plan; patients enrolled in research should be able to say, "I did as I planned," upon reflection. A general notification (e.g., via posters) that all patients will be included in research unless they decline provides no assurance that people will be aware of their ability to decline participation. Since this model of consent cannot satisfy all the conditions of an autonomous authorization, it cannot protect and promote the autonomy of patients enrolled in a pragmatic cluster-randomized trial in any clinical contexts.

Furthermore, the argument that integrated consent, short form consent, and electronic consent can satisfy the conditions of an autonomous authorization implies that these clinical-style consent models can be used to facilitate the conduct of pragmatic cluster-randomized trials in the hemodialysis setting and other clinical contexts. I argue that these approaches differ from simple opt-out consent, as they all seek an intentional authorization from prospective participants and allow health professionals to effectively communicate information about the research to help participants achieve substantial understanding absent control from others. This means that, when the research setting is a clinical setting without research staff, research ethics committees ought to allow health providers to obtain consent using verbal, written, or electronic disclosure processes, provided they are otherwise consistent with regulatory disclosure requirements.

5.5 Future work

There are at least two central questions left unanswered in this thesis that ought to be addressed in future work. First, I argue that a waiver of consent cannot be *broadly* used to facilitate the conduct of pragmatic cluster-randomized trials of individual-level interventions because failing to obtain informed consent for individual-level interventions will constitute more than a minor autonomy infringement. But whether there are *limited* circumstances in which the use of a waiver of consent is justifiable for pragmatic cluster-randomized trials of individual-level interventions is unclear.

Consider the following. Individual-level interventions, such as drugs or vaccines, are directly delivered to patients in research. A waiver of consent should not be granted for these types of interventions because it is a clear violation of a patient's interest in bodily integrity to be given these interventions without their consent for the purposes of research. Hence, granting a waiver of consent for a pragmatic cluster-randomized trial evaluating individual-interventions such as a drug or vaccine would pose more than a minor autonomy infringement. But when, if ever, does not obtaining informed consent for an individual-level intervention pose no more than a minor autonomy infringement? Might there be circumstances in which the autonomy infringement, as a result of not obtaining consent from patients for an individual-level intervention, is minor? For example, a pragmatic cluster-randomized trial could evaluate the comparative effectiveness and cost-effectiveness of two types of surgical suture material (e.g., silk versus nylon) used on patients after they experience a particular injury. While these interventions are directly delivered to patients, it seems outside the scope of patient autonomy to decide which type of suture material can be used to mend their wound. More work is required to delineate when waiving consent requirements for an individual-level intervention constitutes no more than a minor autonomy infringement.

A second question that warrants further investigation is how vulnerable research participants should be identified and protected in pragmatic cluster-randomized trials. Consider the following. Pragmatic cluster-randomized trials aim to include a heterogeneous sample of patients so that their results are broadly applicable to the general patient population. Including all patients who would receive the treatments under investigation as a part of their routine care will likely involve the enrollment of vulnerable people in need of additional protections. According to the Council for International Organizations of Medical Sciences (2016) ethics guidelines, vulnerable groups and individuals are those who "may have an increased likelihood of being wronged or of incurring additional harm" (p.57) by participating in research. Vulnerable research participants may include those who lack decision making capacity (e.g., children, adults with dementia), those in hierarchical relationships (e.g., employees), and institutionalized persons (e.g., prisoners).

My solution to use clinical-style consent models to resolve the conflict between the requirement to respect patient autonomy and the imperative to conduct socially valuable pragmatic cluster-randomized trials provides insufficient protection for prospective research participants who are vulnerable. For instance, an electronic consent process may simply involve the distribution of an electronic device to patients. If a patient suffers from a cognitive impairment, the distribution of an electronic device with information about the trial to obtain their electronic signature will not suffice. Researchers will need to identify those with cognitive impairments (and others who are at an increased likelihood of incurring autonomy wrongs) to offer additional protections. But if researchers hire additional research staff to administer capacity assessments, they may inadvertently undermine the pragmatic aim of mirroring the clinical settings by changing the way care is delivered. Although vulnerable research participants need additional protections, more work is required to understand the degree to which pragmatism is in tension with vulnerability and how the ethical requirement to identify and protect vulnerable participants should be balanced with the aims of pragmatic trials.

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