

Therapeutic appropriation: a new concept in the ethics of clinical research

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Abstract

Ethical concerns about therapeutic misconception have been raised since the early 1980s. This concept was originally described as research participants' assumptions that decisions relating to research interventions are made on the basis of their individual therapeutic needs. The term has since been used to refer to a range of "misunderstandings" that research participants may have. In this paper, we describe a new concept - *therapeutic appropriation*. Therapeutic appropriation occurs when patients, or clinicians, actively reframe research participation as an opportunity to enhance patients' clinical care, while simultaneously acknowledging the generalised research aims. To illustrate the concept of therapeutic appropriation, we draw on data from an interview study which we conducted to investigate the experiences of patients and general practitioners involved in clinical trials in primary care. We argue that therapeutic appropriation has two key elements: comprehension that the research project is not necessarily aiming to benefit participants, together with the deliberate use of incidental features of the research for personal therapeutic benefit of various kinds. We conclude that therapeutic appropriation is a useful concept that refines understanding of potential ethical problems in clinical research, and points to strategies to address them.

Introduction

For more than thirty years, clinical researchers have been concerned with therapeutic misconception. The concept was originally defined as “the notion that... research subjects will assume (especially, but not exclusively, in therapeutic research) that decisions made about their care are being made solely with their benefit in mind”[1]. Despite considerable definitional ambiguity in the literature[2], discussion of therapeutic misconception centres on a concern that prospective and actual research participants be appropriately informed that the research is not primarily – if at all – *intended* to benefit their health. Related phenomena have also been described including therapeutic misestimation and therapeutic optimism[2]. In therapeutic misestimation, which may coincide with therapeutic misconception, research participants may incorrectly estimate potential risks and benefits of their participation in a study, thus believing participation is *likely* to benefit them. In therapeutic optimism, while recognising that a study is not aimed at their personal benefit, participants nevertheless *hope* they will benefit from participation.

The concepts of therapeutic misconception, misestimation and optimism fail to capture a phenomenon we encountered in a recent study investigating clinical trial recruitment of patients by General Practitioners (GPs). Some patients thoroughly understood the research protocol, including the fact it was not intended to benefit them individually. At the same time patients actively sought to use their participation in research to obtain or create opportunities for individual therapeutic benefit, such as additional monitoring, increased access to their GP, opportunities for discussions with additional health professionals, and new pathways to services. We call this phenomenon ‘therapeutic appropriation’ of research. Therapeutic appropriation was not limited to patients; some GPs also engaged in therapeutic appropriation. GPs may actively take advantage of clinical trial opportunities to obtain a variety of benefits for their patients that differ from the explicit aims of the research.

We focus specifically on therapeutic appropriation in the general practice setting, where clinical trials are increasingly being conducted[3-5]. We will use the term ‘patients’ to refer to patients participating in clinical research, and ‘GPs’ to refer to clinicians who were also recruiting for research in this setting. This terminology aligns with the way in which the patients and GPs referred to these groups in our study and with previous research[3]. In the sections that follow, we describe how the concept of therapeutic appropriation emerged from our data and explore the ethical implications associated with it. We argue that therapeutic appropriation *can* constitute an exercise of genuine autonomy, rather than the diminished autonomy of therapeutic misconception, and may benefit patients. However, we show that it is not necessarily an ethically benign phenomenon, and comes with its own distinct ethical risks. Finally, we argue that therapeutic appropriation is a useful concept, because it provides a more nuanced understanding of potential ethical problems in clinical research, which in turn allows for development of strategies to address them.

Therapeutic appropriation in patients' and GPs' accounts of research involvement

We recently conducted an interview study investigating the experiences of GPs and patients involved in research through the primary care clinic. The aim was to better understand the ethical risks that arise when GPs involve their patients in clinical trials. There is reason to believe that the ethical issues associated with dual roles may be different in GP settings, as the doctor-patient relationship is often well established and ongoing, with a great deal of trust invested by the patient in the GP. However, little research on patients' and clinicians' experiences of research participation has been undertaken in primary care. One recent US interview study of clinicians and research co-ordinators reported that "clinicians do not perceive firm distinctions between the roles of clinician and researcher"[3], that clinicians initiate discussions of trials because the pre-existing trusting relationship facilitates recruitment, and that trial participation is viewed as "a means of providing optimal care for the individual patient"[3].

We carried out semi-structured qualitative interviews with nine patients, eight GPs and one research co-ordinator from four GP practices involved in clinical trials in a major Australian capital city. Interviews lasted between 30 and 40 minutes and focused on the recruitment process, decision-making by GPs and patients about their research involvement, and their experiences of research participation. The interview data were coded and organised into common themes, and systematically checked by the research team[6]. The study was approved by the University of Melbourne Human Research Ethics Committee.

When designing the study, we were alert to the possibility of therapeutic misconception, of patients conflating the aims of research with their individual therapeutic needs. Indeed, some interviewees did make statements that suggested they understood their research participation in this way. However, other patients seemed to conceptualise their research participation as an opportunity to enhance their own clinical care, while simultaneously recognising that the purpose of the trial did *not* relate to their individual healthcare. Patient 1, for example, when asked about how he made the decision to participate in the trial, said that he considered: "would it be beneficial for me..., is there some benefits from the participation apart from helping the research itself?". Patient 6 suggested a similar approach:

I thought this is being proactive rather than just being passive in my situation, and hopefully it contributes to results that are helpful for wider needs, this purpose behind it all. As well, I suppose I thought selfishly 'I'll be monitored a bit more thoroughly'...Because if they want this, this trial to work really well then I imagine they would make sure that they're providing that support I need...Part of my mind was thinking 'if I'm on a trial, I'm going to have even more monitoring of my

wellbeing and my health because it's important to them to have good results for their study'.

These patients had an understanding of research as potentially therapeutic but without '*misconceiving*' the purpose of the trial. They understood that the trial was aiming at generating generalisable knowledge that might benefit future patients, but nonetheless they were participating because they perceived aspects of trial participation as potentially beneficial to their individual healthcare. We call this 'therapeutic appropriation'.

Therapeutic appropriation

Therapeutic appropriation occurs when a patient deliberately appropriates (i.e. uses for personal reasons) incidental features of a clinical study to seek personally-defined benefits, while at the same time being aware that the primary aim of the study is not to provide individual benefits to patients. Therapeutic appropriation has two key elements: (i) the deliberate use of incidental features of a clinical trial for therapeutic benefit of various kinds, and (ii) comprehension that the clinical trial is not primarily intended to benefit participants. By 'incidental features', we mean aspects of the clinical trial which are secondary to the intervention (drug, device or program) which the clinical trial is investigating; the relevant benefits are bonuses in nature, and may not be perceived as benefits by researchers. Participants' beliefs about the beneficial impact of specific trial features may be objectively true or false in some cases, for example when a measurable health outcome is associated by participants with increased clinical monitoring during a trial. In other cases, the benefit may be subjective, for example when a patient believes that increased interactions with clinic staff have increased clinician concern for their personal wellbeing.

Therapeutic appropriation can occur at the outset of a study, when a patient is deciding to participate: "I thought if I'm involved in that [trial], my health will be monitored better" [Patient 5] and later on during the study, when it may provide a reason for continuing to participate. For example, Patient 1 described the way in which his involvement in research had changed his relationship with his doctor and the clinic in ways that he perceived as more broadly beneficial to his healthcare:

I feel like I've got better access to my doctor..., and then there's the nurse on the research side. And I almost feel like I've got to know everyone in the clinic a little bit better, like front desk staff and other people. I think out of talking about things like that, I got a care plan and [access to] things that I didn't even know existed or I hadn't thought about.

Therapeutic appropriation is not limited to patients. Some of the GPs and the research co-ordinator in our study described using research participation to improve patients'

healthcare, despite understanding that this was not the goal of the trial. For example, GP5 stated:

I think we actually improve their care and I think patients actually notice it. They find it really helpful that they see [name of Research Coordinator] and have a chance to talk about certain things that maybe they're not comfortable talking to their GP about...It's just an extra person, a different dimension [to the patient's care].

These incidental therapeutic benefits were sometimes communicated to patients during the recruitment process, as indicated by GP1:

[T]hey get a lot of extra testing done nowadays [on the trial]. They get body measurements, they get extra scans, more minerals. Often it gets them extra stuff. So we say 'if you're on the trial, you will get these extra things as part of the routine of being on the trial'.

Distinguishing therapeutic appropriation from therapeutic misconception and other phenomena

Therapeutic misconception occurs when the individual “incorrectly” believes that the study drug (or other intervention) is intended to provide her with clinical benefits. Therapeutic appropriation, in contrast, does not involve such beliefs; it occurs when a patient or clinician perceives additional or alternative benefit in an incidental or secondary aspect of the study protocol, and decides to participate, at least partly, for that reason. The perceived benefit may derive from “clinical” investigations or consultations in the protocol that incidentally provide opportunities for broader assessment of patient health, whatever their intended function in the study. These anticipated benefits may also come from improved quality or frequency of care, but whatever the source, the patient's belief that she will benefit may in some cases be well-founded.

Of course, therapeutic appropriation and therapeutic misconception may coincide; for example, when a patient mistakenly believes potential benefit A is the goal of the research (therapeutic misconception), but also perceives an opportunity to obtain potential benefit B during the course of research participation when B is incidental to the research design. However, the two phenomena differ significantly. Therapeutic appropriation reveals the potentially empowered and autonomous role that patients may take as research participants, making decisions with due consideration of their personal interests and goals in addition to those of researchers. Patients may actively exploit or create opportunities to obtain perceived benefits that are not directly associated with the overarching goal(s) of the research, and which may be recognised as beneficial only from the perspective of individual patient goals and values. In contrast, therapeutic misconception entails impairment to autonomy in the form of a “misunderstanding” of the research goals. Furthermore, benefits

anticipated as a result of therapeutic misconception are, by definition, attributed to the research itself, thus while patients experiencing therapeutic misconception may actively seek to participate in research they believe will be beneficial, once access to a trial is secured, they become fortunate recipients rather than appropriators of any benefits.

Therapeutic appropriation should also be distinguished from the intentional use of incentives to recruit research participants, wherein trial protocols may incorporate benefits for participants designed to motivate participation, and from simple recognition of the benefits embedded in trial protocols and which are directly associated with trial participation. Therapeutic appropriation does not occur when a patient decides to participate in a trial in order to obtain free access to a medication of proven therapeutic value, which is being further evaluated in the trial. It does occur when a patient decides to participate in a trial because her GP clinic reserves regular appointment space for trial participants – intended to enable prompt review of patients with trial-related complications – and she plans to get more swift review of her chronic health complaints which are not related to the trial.

Ethical risks of therapeutic appropriation

Whilst therapeutic appropriation is potentially an exercise of agency and autonomous decision-making, it is not always ethically benign. Therapeutic appropriation can pose ethical risks. The expectation, hope, or desire to obtain therapeutic benefits from incidental features of the protocol acts as an incentive for patients to participate or continue participating. The expected benefits may be genuine ones that provide decision-makers with sound reasons to choose participation in a study, but it is also possible that a misunderstanding or misestimation of the incidental benefits may occur. The first ethical risk is that the incidental effect that the patient believes will be beneficial may in fact be harmful, or its therapeutic value may be over-estimated. For example, an increased frequency of investigations may be perceived by patients as beneficial, but in some circumstances may cause greater harm than good[7]. Second, the perceived incidental benefit that the patient is seeking may represent an “undue incentive”, which again may impair the quality of decision-making. This occurs when the magnitude of benefit appears sufficiently large to distract decision-makers from careful evaluation and consideration of the potential risks of research participation. Third, the perception of incidental benefit may give rise to exploitation, if it leads those in a position of vulnerability to agree to participate in research when the risks from the intervention being trialled outweigh those of the incidental benefits, for example, regular healthcare monitoring, which the patient is seeking to secure.

Although the possibility of deriving indirect benefits from participation in research may seem unlikely to influence decision-making regarding research participation, the quotes above from participants in our study indicate a potentially significant influence. The potential impact of therapeutic appropriation on decision-making is particularly concerning

because the benefits sought in therapeutic appropriation may be less evident to researchers and their potential influence on patients' decision-making may thus be overlooked. Alternatively, where the incidental benefits are recognised, GPs may perceive them as inherently harmless – as a “bonus” of participation. Indeed, as our research suggests, GPs may consciously or unconsciously invoke incidental benefits during recruitment in ways that could strongly influence patients' decision-making. Decision-making that is influenced in this way may impair autonomy, which is considered harmful in itself[8], as well as potentially exploitative in the recruitment setting [9]; it also may lead to decisions that are not in the participants' best interests. There is also the risk (although not demonstrated in our sample) that GPs who are particularly keen to recruit may exaggerate the possibility of indirect benefits to patients.

More broadly, although therapeutic appropriation may lead to genuine benefits for patients, at the clinic level it may adversely affect patients who are ineligible or unable to participate in trials for various reasons. Whether real or perceived, the development of a privileged patient group of research participants with priority access to clinical or research nurses or clinicians may undermine equity across the clinic population. It may also encourage clinicians to rely on research opportunities to address staff shortages in the clinic. The existence of a nurse-researcher in a clinic may provide benefits for the whole clinic population. However, this role may be dependent on ongoing research opportunities and, as it should, at least in theory, prioritise research activities over clinical activities; this may thus represent a less beneficial resource than a dedicated clinic nurse. The benefits gained during therapeutic appropriation may distract from, or undermine clinician efforts to meet the needs of clinics and patients in a more sustainable and equitable manner. Where therapeutic appropriation by patients or clinicians occurs, it should thus prompt reflection on the gaps in healthcare systems and services, which lead to the need for therapeutic appropriation by patients and clinicians.

Responding to therapeutic appropriation in clinical research

We argue that it is essential that GPs are able to recognise and anticipate instances of therapeutic appropriation, so that they can implement systems and strategies to protect against potential risks. These strategies will differ from those aimed at reducing or removing therapeutic misconception, where the problem to be mitigated is misunderstanding of the primary intention of the study and the likely effects of the drug or intervention being studied. In therapeutic appropriation, the ethical risk is the misestimation of the incidental, and perhaps very individually-defined, benefits. Therapeutic appropriation is likely to be strongest where GPs and patients are engaged in a collaborative effort to appropriate therapeutic benefits from a clinical trial. As therapeutic goals align for both parties, this apparent lack of conflict of interest may lull both patients and GPs into a false sense of security, and diminish awareness of potential risks. Establishing a better understanding of the phenomenon of therapeutic appropriation should help GPs to appreciate and

implement safeguards against these risks, as well as optimise genuine opportunities for patients to derive therapeutic benefits from research without compromising their autonomy. The processes of recruitment and seeking consent to participation in clinical trials have traditionally been perceived as the period where clinicians should be most ethically alert; we suggest that this should be replaced with an awareness that decision making in clinical trials is an ongoing process, and that ethical risks may persist or arise at much later points.

We propose that research protocols should explicitly engage with issues relating to therapeutic appropriation, with particular attention to the recruitment period (including recruitment of clinics and GPs) but also at regular intervals throughout trials when opportunities arise to re-evaluate the experiences of patients and GPs. Managing therapeutic appropriation ethically requires a two-step approach. First, identification of potential instances of therapeutic appropriation: when developing or presenting information about the study, risks and benefits should be carefully assessed to determine whether any elements may directly or indirectly raise expectations of incidental benefits. Researchers should be sensitive to the ways in which patients may perceive value in particular activities or practices. Ongoing discussions with participants and GPs throughout a trial will be helpful in identifying elements that have unexpectedly become recognised as opportunities for incidental benefit. Second, the potential influence of therapeutic appropriation on decision-making must be addressed: clinicians and recruiters should actively explore a patient's motivations and goals for participation, and explicitly discuss any benefits the patient appears to be seeking, anticipating or experiencing. Such discussions should aim to ensure: (i) that the patient has an accurate understanding of the real risks and benefits of a particular opportunity they perceive as beneficial; (ii) that any potential benefits are carefully evaluated in the context of other potential benefits and risks of research participation; and (iii) that, wherever possible, the patient is offered opportunities to access the desired benefits without access being conditional upon trial participation, assuming the benefits are genuine and the patient has need of them. Further, measures to ensure disclosure and management of conflicts of interests by researchers, recruiters, or clinicians whose patients are involved in research should explicitly address the possibility of therapeutic appropriation by both patients and clinicians.

Conclusion

We have proposed therapeutic appropriation as a new concept, but this can only be considered a worthwhile exercise if it actually does some ethical work, rather than simply adding a new term to the lexicon. We argue that therapeutic appropriation can be seen as a useful conceptual tool in at least two ways. First, it helps to more precisely identify actual instances of therapeutic misconception, where there are genuine ethical concerns about the quality of informed consent to clinical trial participation because of misunderstanding; this can be distinguished from situations of therapeutic appropriation, where the patient

chooses to participate in order to access secondary or incidental benefits which are real, even if not the intended aim of the trial. In the latter situation there is no undermining of informed consent or autonomy as a result of misunderstanding. Therapeutic appropriation may be done by an empowered patient, purposefully exercising agency, rather than being led astray by ill-founded misconceptions or misunderstandings. Second, recognising therapeutic appropriation sheds light on potential ethical problems in the clinical research context that otherwise might remain hidden. These problems include unrecognised misestimation of incidental benefits, which might be driving agreement to participate in research not founded on true informed consent; and the risk of creating a privileged subgroup of patients who unfairly receive benefits, which ought, as a matter of distributive justice, to be available to all patients. Once these potential problems are recognised, appropriately targeted strategies can be developed to address them. In sum, the concept of therapeutic appropriation expands our understanding of the risks and benefits of clinical research from the perspective of potential participants in ways that can make an ethical difference.

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