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PERSPECTIVE PIECE

Rethinking vulnerable groups in clinical research

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Vulnerable groups are often excluded from clinical research on the basis of scientific, ethical and practical reasons. Although intended to protect vulnerable people and maintain study integrity, exclusion of vulnerable groups from research through use of standard exclusion criteria may not always be necessary and may result in findings that are not generalisable. Achieving a balance between the competing needs to protect vulnerable people and to make progress in our understanding of disorders and their management through research requires a reconsideration of exclusion criteria and consent processes to ensure vulnerable people are appropriately represented in clinical research. Reasons for development of broad exclusion criteria include both concrete barriers and intangible discouraging factors. This paper examines this situation and its consequences, perceived and real barriers to inclusion of vulnerable people in research, and suggests methods for overcoming these barriers and applying thoughtful exclusion criteria.

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Introduction

Clinical research has become an intrinsic part of healthcare systems, resulting in improved health and economic productivity and cost savings (Buxton *et al.* 2004). All citizens are stakeholders in health research (European Commission, 2009) and the burden and opportunity of participation in research should be shared equally among different groups in society. However, research on particular conditions may only be possible in a specific group. Despite their unique needs, groups which are considered vulnerable may be excluded from clinical research for a number of scientific, ethical and practical reasons. Although intended to protect individual rights, exclusion of vulnerable groups from research may not be necessary or desirable in each case. Mental health research is particularly likely to involve vulnerable groups as impaired decision-making capacity, involuntary treatment and social inequality can all lead to vulnerability in research. This paper examines the concept of vulnerability in mental health research, the rationale for exclusion of vulnerable groups from some research and the impact this has on clinical practice. Barriers to inclusion of vulnerable people in research are discussed and suggestions for alternatives to exclusion provided.

Vulnerability

There is a wide body of literature on the definition of vulnerability in clinical research (Rogers, 1990; Council for International Organizations of Medical Sciences, 2007). A broad definition includes all those who are at increased risk of any harm through participation in research. This includes all those who may have impaired decision-making capacity such as those with cognitive impairment or acute mental illness as well as those in unequal relationships who are assumed to have impaired autonomy for example, nursing home residents (Ulrich *et al.* 2002). Some people may be vulnerable by virtue of a circumstance, such as homelessness, as they may have limited choices and therefore place greater value on incentives such as meals, which may result in these groups welcoming trade-offs that others would find unacceptable (Beauchamp *et al.* 2002).

Vulnerable populations in mental health research

In clinical psychiatry research, all potential participants can be defined as vulnerable (Roberts & Roberts, 1999) and many are 'doubly vulnerable' because of a combination of their illness and factors such as detention or involuntary treatment, involvement with third parties such as prison services, or fundamental reliance on health services such as residence in supported accommodation (Kipnis, 2001). Researchers tend to automatically exclude those who are doubly vulnerable (Moore & Miller, 1999) however there is evidence that many common types of research are associated with minimal risk for people with mental illness (Yanos *et al.* 2009). Difficulties in establishing ethical recruitment practices for doubly vulnerable people such as acutely unwell detained patients may have contributed to gaps in evidence-based care, such as in emergency treatment

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(National Institute for Health and Care Excellence, 2015) and treatment of detained patients (National Institute for Health and Care Excellence, 2011).

Importance of access to research

Benefits of research participation

Although only direct health benefits to research participants can be considered by Research Ethics Committees (RECs) (Freedman *et al.* 1992) many participants benefit from research participation in indirect ways, such as feeling heard (McDonald *et al.* 2013). Participation is a strongly positive experience for most (Kost *et al.* 2013) and feeling helpful carries a powerful positive impact (Staphorst *et al.* 2017). Opportunities to be heard and to benefit others may be more highly valued by people in vulnerable groups as they often lack other social engagement opportunities. In a study of dependent drug-injecting participants, the majority cited 'benefit to other individuals or groups' as their reason for research participation (Fry & Dwyer, 2001). Even in research involving potentially distressing trauma-focussed interviews, most research participants report a positive experience and do not regret participation, a finding which remains stable over time (Newman *et al.* 1999).

Patient autonomy

People in vulnerable groups face challenges in research participation, including anxiety about participation and distrust of researchers (Sutton *et al.* 2003) but researchers commonly overestimate the burden of research participation (Willison *et al.* 2009). Lack of involvement in decision-making was identified by detained patients as a major focus of impairment in their dignity and experience of respect during involuntary admission (Chambers *et al.* 2014). As clinicians in psychiatry advocate for patient self-determination in many other aspects of care regardless of illness severity, it is inconsistent not to equally offer research participation to acutely unwell patients.

Barriers to inclusion of vulnerable people

Structural barriers

There is little concrete guidance available to Irish psychiatry researchers on how best to balance protection and inclusion of vulnerable people in research. The Medical Council requires that research be conducted to 'the highest ethical standards' and that informed or substitute consent be obtained in all cases, whereas most international ethical guidelines allow for the requirement for traditional consent to be weighed against practicability, although international ethical guidelines have been shown to be generally inconsistent (Bernabe *et al.* 2016). The emergence of two regulatory systems for research, one for clinical trials (under the European Directive and HPRA, Clinical Trials on Medicinal Products for Human Use Regulations 2004) and one for other research (the REC system), may be a source of confusion, translating into a reluctance to study vulnerable groups, as seen in the United Kingdom (Shepherd, 2016). In many cases, RECs and regulations differ in their requirements (Moore & Donnelly, 2015). While causes for rejection of study protocols by RECs differ for studies recruiting vulnerable *versus* non-vulnerable groups (Adams *et al.* 2013), common reasons for any study protocol rejection by RECs are inadequate consent forms and inadequate explanation of study benefit, and rejection is more likely to be related to ethical problems arising from the relationship between the researcher and participant than from potential physical or mental harm (Olsen & Mahrenholz, 2000). A mechanism to allow people with impaired capacity to partake in research is not specifically addressed in the Assisted Decision-Making (Capacity) Act (Ireland) (Oireachtas, 2015). In contrast, the Mental Capacity Act (England, Wales, Scotland, Northern Ireland) (Mental Capacity Act, 2005, c.9, Part 1, s 30-34, hereafter, the Act), provides an individualised and person-focussed approach. The Act does not specify that there must be a direct benefit to a capacity-impaired research participant in order to partake in research, allowing research participation where research is 'intended to provide knowledge of the causes or treatment of, or of the care of persons affected by, the same or a similar condition', specifically, where the condition is one which has resulted in the impairment of capacity as in the case of psychiatric research. There is an emphasis on risk–benefit analysis in each individual case, as well as a mechanism for third-party assent by carers, which, somewhat uniquely, is phrased as assent on the basis of the capacity-impaired person's likely wishes and feelings. The individual and participant-focussed nature of these recommendations allow for a breadth of research participation within the safeguards provided for by the Act.

Researcher perceptions

A review of research participation of prisoners in the United Kingdom found that the limited access of this group to research was more attributable to researchers' perceptions of the increased burden of including prisoners than ethical concerns or uncertainty about regulations (Charles *et al.* 2016). Preconceptions held by researchers include the belief that people with vulnerability factors are more likely to decline to participate or to drop out than those without these factors, which is not endorsed by clinical trials research

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(de Jonghe *et al.* 2014) or that people who have 'suffered enough' should not be offered research participation (Kleiderman *et al.* 2012).

Participants presenting with risk factors

People who present a risk of self-harm or harm to others are often excluded from research on the basis of unacceptable risk, but exclusion is not necessarily the best way to balance the individual needs of acutely unwell patients for privacy and safety with the need for representative research samples to address clinical questions in these groups. Exclusion of patients who present a risk of self-harm or harm to others results in research which is not representative of patients in mental health services – a systematic review of positron emission technology imaging studies in schizophrenia found that the studies generally included only clinically stable patients (Kirino *et al.* 2017). However, clinical trials in people with dementia successfully recruit participants with severe agitation including physical aggression using alternative consent models (Cummings *et al.* 2015). Arguably such strategies should be applied more often to conduct research with people with acute mental illness who present a risk of physical aggression, as the acute nature of their illness, unlike a progressive disorder, indicates that are likely to regain capacity, making this a population which is suitable for deferred consent. Safety is a primary concern, but for patients who experience suicidal ideation or thoughts of self-harm, research participation (including repeated assessment of suicidality) is not associated with an increase in thoughts of self-harm or suicide (Eynan *et al.* 2014).

Barriers unique to minors

Research which involves people under the age of 18 requires obtaining the minor's informed verbal or written assent as well as the informed written consent of a third party, for example guardian. In Ireland, people between the ages of 16 and 18 can consent to medical treatment as adults (i.e. without third-party consent), but it is unclear whether refusal of treatment or consent to research participation is similarly allowed, and for now research participation requires both the young person's assent and guardian consent. In some other jurisdictions (USA, UK), a mature-minor clause allows those over the age of 14 who have decision-making capacity to make autonomous decisions on matters such as research participation (Sigman & O'Connor, 1991). It has been argued that if decision-making capacity is present in a young person, their wish to take part in research should not be dependent on another's agreement (Sanci *et al.* 2004). There is no international consensus on the best research ethics review guidelines for research involving mature minors, and academic RECs report feeling inadequately expert at reviewing such research (Office of the Minister for Children and Youth Affairs, 2010). It has also been reported that there is both over- and under-estimation of risk and vulnerability in research involving minors (Office of the Minister for Children and Youth Affairs, 2010).

Capacity

The threshold of capacity required to make decisions about research participation will vary according to the risk or burden associated with the study. Mental health researchers will be familiar with the statutory standard, a functional assessment of time- and decision-specific capacity (Oireachtas, 2013). Global indices of cognitive function such as the standardised Mini Mental State Exam are not predictive of decision-making capacity (Marson *et al.* 1995) and capacity assessment tools have, in general, been found to be inconsistent (Gurrera *et al.* 2007). There is thus no universally acceptable method of assessing decision-making capacity to obtain ethical approval (Schwenzer, 2008), however the MacArthur competence assessment tool for clinical research (MacCAT-CR) is a commonly used instrument (Appelbaum *et al.* 1997). Assessment of decision-making capacity requires deciding which factors must be present to show a potential participant is not at risk of coercion as well as deciding what degree of variation from commonly held beliefs will be accepted. In addition, to avoid mislabelling of common human irrationality as incompetence, an assessment of decision-making capacity should seek to understand the potential participant's logic in coming to their decision. The MacCAT-CR incorporates these elements in a flexible tool which can be modified for a variety of types of research, and has been studied in numerous settings with patients with various mental illnesses (Appelbaum, 2006, 2007; Wang *et al.* 2016). Many research groups will not have an independent, experienced clinician willing and available to conduct capacity assessments and may resort to excluding all those who have risk factors for impaired capacity.

Exclusion criteria

Rationale for exclusion criteria

Exclusion criteria are necessary in all studies to protect the scientific quality of the study design by ensuring the study sample is specific to the disorder being examined. They also act as gatekeeper devices, protecting vulnerable people from unnecessary risk due to inappropriate inclusion in research. Often researchers may have to sacrifice the representativeness of their study sample (*v.* the target population) to achieve a relatively

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homogenous study sample for the purposes of making meaningful comparisons between groups. However, this can result in exclusion criteria becoming a standard set of barriers to research participation for potentially large groups of people, such as those with cognitive impairment or those who live in nursing homes (Hall *et al.* 2009). In some research areas such as traumatic brain injury, the negative consequences of broad research exclusion have been recognised and strictly minimised exclusion criteria are already recommended (Maas *et al.* 2010). Often the justification for exclusion is unclear – in one review, 84% of trials published in high-impact medical journals had at least one poorly justified exclusion criterion (Van Spall *et al.* 2007).

Representativeness

Although some exclusion criteria are necessary for design reasons, broad exclusion criteria may do more harm than good, resulting in study samples which may be inadequate or do not reflect the range and complexity of patients seeking treatment. This is a problem for all medical disciplines, such that it has been identified in an EU Regulation due for operation in 2018 (European Parliament, Council of the European Union, 2014), but has been repeatedly demonstrated to be problematic in psychiatry research. A review of interventional studies in schizophrenia found that 80% of patients with schizophrenia would be excluded from such studies, particularly women, older people and those with more severe illness, making such studies poorly generalisable to clinical populations (Humphreys & Weisner, 2000; Humphreys, 2014). Exclusion criteria from two large trials in Alzheimer's disease would have excluded 94.8% of clinical registry patients from participation and those who were excluded had similar cognitive functioning compared with those who met inclusion criteria (Schneider *et al.* 1997). Studies of patients with epilepsy where psychiatric comorbidity is an exclusion criterion have been shown to be poorly representative of the target population and aside from psychiatric comorbidity, excluded and included groups are otherwise similar at baseline (da Conceicao *et al.* 2013).

Methods to facilitate inclusion of vulnerable people

Consent processes are the focus of much ethical review – comments on consent processes arose in 80% of applications to RECs in one review (van Lent *et al.* 2014). Most RECs will be familiar with the alternatives to traditional informed consent, which will be outlined below. For example, the US National Institute of Neurological Disorders and Stroke has formally encouraged epilepsy researchers to accept surrogate consent as well as patient consent (Fertig *et al.* 2014).

Traditional informed consent

The current model of written informed consent, although encouraged by research stakeholders, may not be ideal even for participants who have no vulnerability factors. A substantial proportion of consented participants have poor comprehension of research goals and methods (Misra *et al.* 2008; Rose *et al.* 2013). There is a strong correlation between therapeutic misconception (belief that an investigative treatment will have a therapeutic effect) and willingness to participate in clinical trials (Reijula *et al.* 2015) and even in studies where participants rate their satisfaction with the consent process as 'high', the quality of consent may be poor (Pentz *et al.* 2002). Although research documents require REC approval, many clinical trial documents still do not meet the information needs of participants (Hietanen *et al.* 2000) and participants do not identify consent procedures as being for their benefit (Verástegui, 2006). Consent forms arouse suspicion and reluctance in participants who are willing to participate in research but not keen to sign a document (Gysels *et al.* 2008). Many of the difficulties with accurate and adequate (but not overwhelming) trial information could be overcome by emphasising face-to-face communication (Locock & Smith, 2011). A multi-stage process of information-giving, questions and consent has been suggested as being more appropriate for vulnerable people (Beauchamp *et al.* 2002).

Assent to participation

Passive assent or mere absence of objection to research participation is unlikely to be an acceptable alternative to traditional informed consent for studies involving people with mental illness, regardless of study design, though it should be borne in mind that for any of the alternative consent models, assent is required on an ongoing basis, as objection to participation by the participant negates any consent procedure. Additionally, as capacity to consent can fluctuate with improvement or deterioration of the mental state, researchers should have a method for frequent reassessment of capacity and consent throughout participation.

Enhanced informed consent

Enhanced informed consent refers to traditional informed consent with additions such as decision-making support from a family member or independent advocate, provision of information in multiple media and provision of additional time and researcher contact for information-giving sessions. Many of these methods are already employed by clinical researchers in psychiatry when approaching participants who have intact decision-making capacity but may have slowed

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thought processes, or difficulty concentrating and making decisions due to mental illness. Supporting decision-making capacity in these ways is an acceptable enhancement to the traditional consent model for studies where there are no conflicts of interest and researchers are trained to be vigilant for the risk of persuasion. The study protocol should contain details about assessment of decision-making capacity, such as a formal or functional assessment, and how researchers will prevent and recognise overburdening of participants or their families. This approach may be the least controversial alternative to traditional written informed consent but may incur additional costs as more researcher time and greater flexibility may be required – visits to patients at their best time or when family members are visiting may be outside regular working hours. However, this approach has resulted in high levels of comprehension and participant retention among vulnerable groups (Vallely *et al.* 2010).

Proxy/substitute/third-party consent

Substitute consent is the most standard alternative to traditional consent and in Ireland is governed by a pragmatic framework where a person with a close relationship with the participant can provide consent on their behalf in certain situations. The Irish Council for Bioethics advises RECs that substitute consent can be used in studies recruiting children, individuals with an intellectual disability or with short- or long-term unconsciousness where research participation is clearly in the person's best interests or carries minimal risk or impact (Irish Council for Bioethics, 2004). The Declaration of Helsinki more broadly states that substitute consent can be appropriate for all those who are incapable of consenting to research, as do other international guidelines (European Council, 2001; World Medical Association, 2001; Council for International Organizations of Medical Sciences, 2007). In some countries where a court-appointed representative is required to obtain consent there have been detrimental effects on research progress in mental health (Porteri & Petrini, 2015). Most of those acting as next-of-kin for involuntarily detailed patients welcome greater use of substitute decision-making, including for research (Førde *et al.* 2016). However, substitute consent may not provide appropriate safeguarding of patients' interests where the threshold of personal acceptability of a treatment is unclear to the third party providing consent or if a patient cannot self-report symptoms or communicate adverse effects in interventional studies (Gysels *et al.* 2008). Substitute consent has thus been demonstrated to be particularly problematic in dementia research (Roberts, 1998). Deciding on the source of substitute consent depends on the circumstances and it has been suggested that for low-risk or non-interventional studies, a community member or patient representative may suffice (Welch *et al.* 2015).

Retrospective consent

Deferred or retrospective consent is commonly used in other medical disciplines where transient illness results in a temporary impairment in capacity to consent, such as in emergency presentations and intensive care research. As such this model is well-suited to researching the needs of acutely unwell psychiatric patients, the vast majority of whom will regain capacity with successful treatment. This model involves identifying eligible participants, proceeding with study measures, and regularly assessing capacity to consent. Immediately upon return of capacity, the informed consent process should begin. If the participant consents to their participation in the study, they will continue to be included, and if not, study measures will be discontinued and in addition, their data should be withdrawn from the study. Unless it is clearly impracticable, it is strongly recommended that substitute consent from a family member or other third party should be additionally obtained during the period of loss of capacity. Where deferral of consent proceeds without substitute consent in an emergency, this should be sought as soon as possible (World Medical Association, 2001). The threshold for acceptable risk is low where deferred consent is in place, and for interventional studies, the non-experimental treatment arm must be at least usual care, not placebo. Clinicians' attitudes towards this type of consent become increasingly positive with greater experience with the model (Woolfall *et al.* 2013). Deferred consent has been successfully used in several clinical trials in psychiatry, particularly in acute treatments, and crucially, this method has been found to facilitate the recruitment of participants who are highly representative of the target population (Conus *et al.* 2015).

Exception from informed consent

This consent model has been employed in dementia, neurological research and emergency medicine (Yamal *et al.* 2014) as a recognition that in some limited circumstances, research exclusion is not always in the best interests of people who cannot provide informed consent, and is endorsed in these limited circumstances by the Declaration of Helsinki. Surveys of research without consent found that half of the members of the public asked about this practice inherently disagreed with it but a higher percentage would actually be willing to take part in such a study (Lecouturier *et al.* 2008).

Recommendations

Diversifying methods developed to address ethnic, age and gender disparity in clinical trials (UyBico *et al.* 2007)

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could be adapted to address the problem of exclusion of vulnerable groups from clinical research. A strict approach to designing and applying exclusion criteria where participants are deemed 'eligible until proven otherwise', will ensure researchers stay vigilant to the need for representative and generalisable samples. Individual rather than whole-group application of exclusion criteria should be used to identify truly vulnerable participants. In addition, for some of those identified as vulnerable, alternative consent processes will still allow for participation, although a systematic and explicit risk–benefit assessment should be documented. Exclusion should be seen a last resort, where, for example, rather than excluding people with suicidal ideation, researchers could be trained to monitor the progress of suicidal thoughts and use a protocol for action if heightened risk is identified. Grant and REC applications should require justification of exclusion criteria and journals should require details of efforts made to include vulnerable people and ensure the study sample is generalisable. Basing researchers within the target community (e.g. for studies of prisoners with mental illness, research based in prisons) and fostering collaborative responsibility by enhancing public and patient involvement in research planning (a major focus of the current Health Research Board research strategy) could help to broaden inclusion. As RECs bear the burden of systematic oversight for clinical research, greater involvement of people with vulnerability factors in RECs should be considered and additional training provided to REC members on alternative consent models and the importance of balancing protection of participants from harm with protection from exclusion. Although some resources are available to guide researchers (Li *et al.* 2016), an Irish-specific resource would be of benefit to assist researchers dealing with vulnerable groups to navigate research regulation processes.

Discussion

Membership of a vulnerable group does not indicate that an individual does not have capacity to decide whether or not to participate in a particular study (Appelbaum, 2006; Morán-Sánchez *et al.* 2016). Yet members of these groups, many of whom have unimpaired decisional capacity, are often routinely excluded because of their diagnosis or situation (Frew *et al.* 2014; Head *et al.* 2015). Group exclusion may result in studies that are not representative of the target population, which in turn translate into uneasy, unsatisfactorily informed prescribing decisions. Clinical guidelines as well as health service funding decisions are based on best available evidence. Where best evidence has broadly excluded vulnerable people, clinicians unknowingly make prescribing decisions based on evidence that is not generalisable to or representative of the patient in the room. Researchers may lack confidence in separating those who are truly vulnerable from those who can be facilitated to participate, or perceive inclusion of potentially vulnerable people as simply too much work. In the past, research ethics largely focussed on a paternalistic approach which valued the protection of vulnerable people above other concerns. Although there is now a greater emphasis on inclusion and fair access to research participation, clinical researchers accustomed to paternalistic research ethics models may not give due weight to the risk of creating unfair participant selection when assessing whether the benefits outweigh the added work involved in including vulnerable groups. Adding safeguards such as an individual assessment of decision-making capacity prior to participation, or increasing time for provision of study information may seem burdensome. However, the current approach of applying broad exclusion criteria requires screening of more potential participants which results in longer recruitment periods and requires more staff.

Conclusion

For real advances to be made in mental health research (and consequently mental health services), individuals who are classified as vulnerable need to be included in research and in order to achieve this, we need to move beyond traditional research design and to employ more innovative safeguards. Rethinking standard exclusion criteria will result in more generalisable research, more new research targeting unmet needs, and greater fairness in study participant selection. While it may be more difficult to communicate, implement and realise non-traditional informed consent processes when recruiting patients with mental illness, making progress in unmet needs requires a change from current approaches.

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Ethical Standards

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relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008.

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