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Introduction

In this paper we outline the concept of therapeutic misconception (TM) and its implications for informed consent in the context of clinical trials for childhood diseases. Although TM has been well described (Miller and Joffe, 2006), it has not been considered in the context where parental consent is a requirement. In this situation, it is often the parent who is vulnerable to TM. Drawing upon our experience of translational research in rare diseases, we consider the wider environment in which the value of research is promoted as well as the particular circumstances of clinical trials. The information component of informed consent is significant for the research participant, yet little attention has been paid to the wider sources of information and influence that parents may draw upon when making their decision. It is evident that in the rare disease context there is an important role played by the patient advocacy groups as sources of information, alongside clinicians and trial co-ordinators. There is no doubt that the influence of advocacy groups has been, and continues to be a positive one in terms of advancing the cause of people with rare, chronic, life-limiting disease. However, we also recognise that TM may be embedded within the patient advocacy approach to the promotion of research to the extent that the treatment/research distinction becomes blurred. Balanced against this, we also consider the opportunity such organizations present to overcome TM through a process of co-operation and collaboration between them and the researcher that goes some way towards ameliorating the challenges of ensuring that the risks as well as the benefits of research are explained adequately.

Acknowledging the conflicting forces at play for patients, parents and researchers, we explore the role of hope, trust and scientific ambition as factors within the complex research context. TM is regarded as highly relevant to the concept of a legally valid and ethical informed consent that is the necessary gateway to involvement in research. The volumes of literature on consent (Faden and Beauchamp, 1986, Doyal and Tobias, 2000, and Manson and O’Neil, 2002) have already established the problematic nature of consent, yet it remains both central to, and necessary for ‘ethical’ research, as well as being a legal requirement as our focus on the UK position demonstrates by way of example. We acknowledge that research which requires participants who are also patients with life-threatening conditions, presents particular challenges, even more so when those patients are children and require parental consent. It is clear that in such circumstances consent processes can appear too fragile to withstand all of the ethical work they are required to do. Nevertheless, we conclude that consent should not be abandoned.

The focus of this paper has been undertaken under the aegis of Translational Research in Europe – Assessment and Treatment of Neuromuscular Diseases (TREAT-NMD) which is a European Network of Excellence formed to advance diagnosis and care, and develop new treatments for neuromuscular disorders (NMDs) (TREAT-NMD, 2010). There are over 60 neuromuscular conditions, most of which do not have an effective treatment (Pohlschmidt and Meadowcroft, 2010). In this paper we make particular reference to Duchenne Muscular Dystrophy (DMD) which is one of the most common genetic disorders affecting children and young adults with one in every 3,500 boys born worldwide affected. DMD is a severe, progressive muscle-wasting condition which presents in early childhood and patients become wheelchair-dependent in their early teenage years. Without treatment, DMD causes death in the early twenties. The social and emotional costs are considerable, and families report care

burden and support issues, isolation, social inequality and psychological stress and depression (Gagliardi, 1991; Ahlstrom, and Sjoden, 1996; Abresch, Seyden et al, 1998; Eggers and Zatz, 1998; Natterlund and Sjoden et al, 2001; Bothwel, Dooley et al, 2002; Bostrom and Ahlstrom, 2004; Boyer, Drame et al, 2006 and Gibson, Young et al. 2007). There is now a well-established international network of patient organizations that are well-informed, experienced lobbyists and effective fundraisers. These organizations have been pressing for research leading to treatment for neuromuscular diseases and have entered into partnerships with researchers and clinicians. There are several compounds entering clinical trials for DMD, but these are still a very early step in the translational process from laboratory to clinic. It is in this context of the promise of an actual therapy for DMD, that concern about TM has been raised.

Addressing the issue of parental consent to research is both important and timely because the European Commission is keen to address the lack of research into drugs used to treat children (Sammons 2009). The dearth of research involving children is ethically untenable because they cannot be assumed to be receptive to adult drug formulations (Stephenson, 2005). Although 10 – 20 per cent of drugs prescribed for children in general practice are unlicensed for use in children, this figure rises to 45 percent on general paediatric wards and to over 90 per cent in neonatal intensive care (Parliamentary Office of Science and Technology, 2006). For children with DMD the situation is even worse and the population is reliant upon innovation specifically targeted at their condition. There is now European legislation encouraging drug companies to undertake appropriate research for childhood conditions so that their therapeutic needs are more directly addressed (for example, Regulation 1901, 2006, Regulation 1768, 1992, Directive 2001/20/EC and Directive 2001/83/EC). The legislation will increase information available to the patient/carer and

prescriber about the use of medicines in children, including clinical trial data. These objectives will be achieved through a system of requirements and incentives, overseen by the Paediatric Committee sited at the European Medicines Agency (EMA). These paediatric-specific provisions work alongside the framework that regulates the use of modern, biotechnological medicinal products. For example, Regulation 726/2004 established the EMA responsible for the authorization and supervision of medicinal products for human and veterinary use following scientific evaluation of the quality, safety and efficacy of the product. It creates a single European authorization process for the placing of advanced therapy medicinal products on the market and potentially allows faster and safer access to treatment for patients who suffer from diseases that have, until now, been incurable. This Regulation will cover new forms of treatment including advanced therapy medicinal products, such as gene therapy, somatic cell therapy and tissue engineering. Articles 6(7), 9(4) and 10(6) of Directive 2001/20/EC deal with clinical trials relating to these therapies. These initiatives are likely to have a major impact on the biotechnology and medical research industries, and will play a large part in determining the direction that European medical research takes in the future.

The European legislation also presents an opportunity to exclude unethical therapies from the marketplace: the EMA market authorization will only be granted if the product satisfies scientific evaluation of quality, safety and efficacy of the product. It will also have to reach the high ethical standards of the Clinical Trials Directive (Directive 2001/20/EC) at its clinical trial stage. There will be a need for rules to be developed to ensure good clinical practice in investigations involving advanced therapy medicinal products because of their specific technical characteristics (*ibid.* and Article 4(2)). Thus, from a regulatory perspective, the process of bringing new drugs to the market will be rigorous. This system of governance

should ensure that participants in research are not subjected to undue risk. However, in our view, the level of risk involved is independent of the fact that consent ought to be voluntary and informed. Since it is likely that rare diseases will be the subject of advanced therapies research, then the challenge of explaining these experimental therapies will be all the greater. The precautionary tone regarding the inclusion of children in clinical trials (for example, para. 3) suggests to us that particular care is needed to ensure that parental consent procedures are rigorously managed.

With this European legislative context in mind, the next section explores what is meant by TM.

What is TM?

The phenomenon that participants in clinical research often have a poor understanding of the purpose of the research has been thoroughly explored elsewhere (Kodish et al, 2004 and Siminoff and Simon, 2004). Appelbaum and colleagues were the first to consider the ethical implications of a particular form of misconception, the *therapeutic* misconception (TM), when they observed that patients with mental health disorders, involved in randomised clinical trials, believed that the trial drug was given with the same therapeutic intent as the other treatments provided by their doctor (Appelbaum, Roth et al, 1982 and Appelbaum, Roth et al, 1987, Appelbaum, Lidz and Grisso, 2004 and Henderson et al, 2006). This literature reveals that there are many misconceptions amongst research participants about the nature and purpose of research including the meaning of such terms as ‘randomisation’ and ‘placebo’. However, TM may be held independently of other misunderstandings about

research. For the purposes of further scrutiny of the phenomenon of TM, Henderson et al proposed the following definition:

Therapeutic misconception exists when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial.

(Henderson et al, 2007, p. 1736)

However, in line with the views expressed by the National Bioethics Advisory Commission (2001), we suggest that if trial participants, or those consenting for them, believe that the central purpose of the specific trial is therapeutic and that the individual subject will personally benefit from participation, then this false belief may motivate them to participate, and in extreme cases may disqualify their consent. At first glance, the ethical import of TM lies in the significance it has for a person's capacity for autonomy, including their ability to weigh the risks of participation in proportion to benefits. If there is a false belief in the direct benefit of the research, then the implication is that less weight will be given to the risks of participation. Before exploring the ethical implications in more detail we shall examine a number of factors that have a bearing upon the TM.

Factors in Therapeutic Misconception

The factors that foster TM are multiple, often subtle and complex. One of the influential factors in the wider context is the way in which public perception of medical science is influenced by the public face of science. A broad programme of research such as human embryonic stem cells (hESC) research is widely discussed and publicly 'hyped' in the media representations of the science (Williams-Jones and Corrigan, 2003, Horrobin, 2003, and

Braude et al, 2005, Geesink et al, 2008, Woods 2008). In addition, as Dresser observes, celebrity endorsement of stem cell science can be very influential (Dresser 2002).

Christopher Reeve, the actor who suffered a spinal cord injury, was just such a prominent advocate of hESC science and, rightly or wrongly, was associated with a belief that stem cell science was close to delivering a cure (CRF, 2005). A consequence of public misconceptions about the stage at which hESC is currently at, has been the growing unethical trade in so-called ‘stem cell therapies’ (Sorapop and Douglas, 2009). Parents of patients with rare diseases such as DMD can be vulnerable to exaggerated claims and deliberate mis-selling of such technologies as established therapies. (TREAT-NMD Project Ethics Council, 2010)

In the UK, the Department of Health’s publication, *Stem cell research: medical progress with responsibility* (DoH, 2000), was cautious but optimistic about the longer-term future of stem cell science, yet the major investment into stem cell science within the UK has led to high expectations for short-term benefits (Braude et al, 2005). Another source of elevated expectation stems from the competitive research funding environment which means that bids for funding have to be ‘pitched’ to funders, and the accompanying public message is often the same one of short-term benefit for specific diseases (Geesink et al, 2008). The families of patients, and patients with DMD, are particularly sensitive to any news of a possible therapy. Patient organizations operate websites that constantly update members on news of clinical trials, promising compounds and any hopeful new development (Action Duchenne). These same organizations often seek collaboration and support from pharmaceutical companies and academic researchers who are yet another source of information (Muscular Dystrophy Association, Parent Project Muscular Dystrophy). This is not to say that patient organizations are deliberately misrepresenting the stage of scientific development, but often information can be present information with an underlying hint of

optimism easily identified by those with a disposition to hope in a biotechnological solution. Martin and Nightingale (2004) have argued that the promises of the so-called 'biotech revolution' are in general over-blown: '[m]any expectations are wildly optimistic and over-estimate the speed and extent of the impact of biotechnology' (p. 564). Information that aims to foster hope and aspiration can so often be misrepresented as fact, particularly when there is poor attention to the language in which these discussions take place. Such is the faith invested in a solution through biotechnology that there is the potential for a 'collective therapeutic misconception' that fosters collusion in a highly optimistic belief in a biotechnological solution (Dresser, 2001 and Dresser, 2002).

Several commentators have also remarked upon the implicit collusion that can occur between the researcher and the research subject (Appelbaum et al, 1982, Dresser, 2002, de Melo-Martin and Ho, 2008). There are several factors involved. One is related to the psychology or social conditioning of patients, or their parents, whose relationship with a clinician is framed by expectations for personal care (Joffe et al, 2001, Appelbaum et al, 2004). In the research context the physician who acts as a personal doctor providing care may also be working in a dual role as both physician and researcher but in circumstances in which the differences between those roles are not clearly understood by parents and patients (Bamberg and Budwig, 1992 and Hadskis et al, 2008). As de Melo-Martin and Ho (2008) observe, trust is an essential element in an effective clinical relationship but is also necessary in the research relationship. However, they argue that the grounds for trust differ between the clinical and the research context but that these grounds can become blurred when one person is playing a dual role. Even though the physician in his or her capacity as *researcher* may act with integrity, the distinction between the roles of clinician and researcher is often too subtle for patients to appreciate, a situation that is not helped by the common practice of research

being described in therapeutic terms such as when an experimental substance is described as a new 'treatment'. Henderson (2008) found that parents of DMD boys who had developed trust in their physician also turned to them for guidance when it came to making research decisions, often taking the physician's outline of the research for which their child may be eligible as a recommendation to join the study rather than the description of the study. This echoes findings reported elsewhere (Dresser, 2002). Clinicians are also subject to similar psychological pressures because they are often deeply involved with the families they care for which may influence their capacity to separate their different roles as clinician and as researcher (Bamberg and Budwig, 1992 and Miller, 2000). It can also be difficult for individuals to separate the emotional from the rational in a context in which they are also passionately involved in the issues. This may be as true for clinicians and researchers as it is for patients and parents (Reynolds and Nelson, 2007 and Dixon-Woods et al 2007). We would suggest that there is therefore a need to carefully mark out the 'informing' procedure from the clinical consultation though clinicians often contend that they are the most appropriate person to discuss research with their own patients (Personal communication, Straub, 2010). We also appreciate that finding additional time in which to discuss research with patients can add pressure to a clinician's already busy schedule.

Having examined some of the key factors that can influence TM, the following section outlines the UK's legal approach to informed consent with a view to setting out the legal and moral duties of the researcher as well as those of the parent where parental consent is required. The question then is how the notion of TM with respect to research should be addressed to avoid an infringement of the law.

The Legal Framework in the UK

As noted above, that there should be free and informed consent to any biomedical intervention as a condition of good clinical practice has widespread agreement in international codes of ethics, human rights instruments and, in some jurisdictions, domestic law. To take the UK example, the Medicines for Human Use (Clinical Trials) Regulations 2004 (Regulations 2004), which gave force to the EC Clinical Trials Directive, strengthen any claims made by a participant that this requirement has been breached (Schedule 1, Part 3). The Regulations give rise to potential civil and criminal liability but do not demand the same level of detail as some professional guidance (for example, General Medical Council (GMC), 2002, paras. 19-21) and international instruments (for example, the Declaration of Helsinki, 2008, para. 22) to satisfy informed consent requirements.

The Regulations require that a legal representative, unconnected with the trial, must give informed consent on an incapacitated person's behalf (Schedule 1, Part 1, para. 2 (incapacitated adults) and Schedule 1, Part 4 (children). For children under 16, this will be someone with parental responsibility as provided by section 3(1) Children's Act 1989 (CA). Provided children over 16 satisfy the requirements for competency under section 2(1) of the Mental Capacity Act 2005 (MCA), they will be able to consent for themselves and every possible means must be used to support the individual to make their own decisions (section 1(3) and Code of Practice, Chapter 3). Where a proxy is unavailable or unwilling to act in this capacity, the participant's doctor may act as the legal representative provided they are unconnected with the trial. If this is not possible, the relevant NHS Trust may nominate someone else to act as the legal representative provided they, too, are unconnected with the trial.

A parent or legal representative must act on the basis of the 'presumed will' of the incapacitated patient with all the inherent difficulties this concept entails, given that it may not be based on past or current expressed will (Schedule 1, Part 4, para. 13 (child) and Schedule 1, Part 5, para 13 (incapacitated adult). Although such devices may import a level of fiction into the calculation they are nevertheless an important indication of the extent the law is prepared to go to factor in a level of respect for self-determination. The interpretation of legal requirements will be subject to the rules of statutory interpretation and, where relevant, judicial decision-making through the common law. Ethical guidance will also be interpreted through the common law where necessary. Where the common law is engaged, the principles established in case law on medical treatment will need to be distilled and applied by analogy to the research context, given the paucity of directly relevant cases. Parents must act in their child's best interests (*Gillick*, 127). A wide reading is now given to best interests, which encompass medical, emotional and other welfare factors (*Re A* 2000, 555), including the psychological and social benefits (*Re Y*, 1997, 562), so this should include allowing children to influence what happens to them as much as possible (GMC, 2007). It is arguable that all that a parent is required by the law to do is act in a way which is not against a child's best interests (*S v S*, 1972). Following that principle would give parents authority to consent to certain non-therapeutic interventions on their children (Pattinson, 2011, p. 185). In the event of a conflict, a court must decide what is in the child's best interests (*Glass*, 1999) and regard must be had to the wishes and feelings of the child concerned as far as they can be ascertained according to their age and understanding (section 1(3)(a) CA) but it has been argued that the courts are only too ready to deny children's agency under the cloak of welfare discussions (James, 2008).

A researcher may be liable to certain legal claims such as a claim in trespass to the person where consent to research procedures is judged invalid because of a failure to disclose sufficient information about an intervention. A valid consent requires that the person (or their proxy) is legally competent, their decision has been made free from coercion and that they are broadly aware of the proposed intervention (*Chatterton, 1981*). It is certainly conceivable that a researcher who encouraged TM may be considered as having breached the standard of reasonable disclosure. A research participant may also have a claim available in negligence *where they have suffered harm* (*Sidaway, 1985*) as a result of their participation in research. This is in addition to any action that arises under the Regulations or in trespass to the person where the basic requirements of a valid consent are not met. Actions in negligence are challenging for claimants and will only succeed if the doctor has breached the *Bolam* (1957) standard as to what a reasonable doctor would have disclosed in the same circumstances, subject to the *Bolitho* (1998) requirement that medical opinion should be capable of withstanding logical analysis. Information should now be disclosed where there is a significant risk of harm that would affect the judgment of a reasonable, prudent patient (*Pearce, 1999*). It is likely that there would be liability in battery and negligence if the researcher failed to disclose the intervention was experimental or mainly for research purposes. The courts have exhibited a growing tendency in favour of patient's rights to information (*Chester 2005*). In addition, doctors cannot rely on their 'therapeutic privilege' (*Sidaway, 1985*) to decide it would not be in a patient's best interests to be made aware of research information. In deciding the appropriate standard of disclosure, courts are likely to take account of national and international guidance and these are very clear on the need for detailed disclosure. In practice, the information provided for research participants undergoes several rounds of scrutiny not least of which by the Research Ethics Committee (REC). Researchers are also encouraged to involve patients at an early stage in the development of

the research protocol and to take advantage of patient scrutiny of the information materials under development. A prudent researcher who has consulted and taken advice at various stages in developing information for participants would be less vulnerable to the scrutiny of the courts.

Notwithstanding this trend, difficulties remain in the research context. These include ascertaining what was known about risks at the time the research was conducted and the degree of latitude allowed to health professionals on disclosure by the *Bolam* standard even with the *Bolitho* caveat. Establishing the causal link between the undisclosed risks and the eventuating damage is always problematic. Proving the research subject would have opted not to participate had they been aware of the risks is also difficult notwithstanding the decision in *Chester*. Overall, there is widespread agreement that in the case of non-therapeutic treatment, the level of disclosure should be much higher than that expected with respect to treatment. For example, in the US, the failure to disclose risks has even been held to violate the fundamental right to life and liberty under the due process clause of the Fourteenth Amendment of the Constitution (*Re Cincinnati Radiation* 1995).

Of course, all relevant information pertaining to a study needs to be understood by the participant or their representative, and the GMC's guidance is particularly helpful in this regard (GMC, 2002). It stipulates that the information that the patient wants or, importantly, 'ought to know', should be 'presented in terms and a form that they can understand' with detailed guidance as what this might be, including allowing for time to deliberate on the implications of participating in research (paras. 19-21). The guidance is also useful in that it stipulates that doctors must not put pressure on volunteers to participate in research and must ensure that no real or implied coercion is put on those in a dependant relationship (*ibid.*). This

approach is echoed in its *Good Practice in Research* (2010). The GMC has now published specific guidance on ways in which communication with children may be enhanced (GMC, 2007). It must not be forgotten that professional guidance provides a useful benchmark for the courts to consider in any allegation of breach, and referral to the GMC is an option for the aggrieved who cannot or do not wish to pursue litigation. Breach of this guidance may result in disciplinary action. Following the GMC guidance seems to us to be an example of making reasonable endeavours in seeking informed consent. A court is unlikely to ask for more. Of course, notwithstanding these efforts, TM may still be operating.

Although there has been some consideration of the circumstances in which those who lack the mental capacity to consent may be included in a clinical trial by the proxy consent of their legal representative, perhaps the least controversial of these proxies remains the parental consent for a child. Even here there are concerns because many regard children as the most vulnerable research participants and therefore the level of protection required by society is greatest. While a cautious approach is entirely appropriate, especially when we consider that unethical research has been undertaken in the relatively recent past (Hagger, 2009, Chapter 7), it is also important to protect the competent child's right to decide about participating in research (Hagger and Woods, 2005, Hagger *ibid.* and Cave, 2010). Achieving the right balance between protection and empowerment is a difficult task for RECs who must approve proposals for clinical trials in conjunction with the Medicines and Healthcare Products Agency given the array of disparate ethical and legal guidance. The Regulations 2004 may be perceived as being particularly restrictive because of the requirement for consent only from a legal proxy with respect to children under 16 although the originating EU Directive is more ambiguous (Art. 4(a)). The position of the Regulations 2004 is at odds with developing case law which increasingly acknowledges children's right to autonomy as provided by Article

8(1) of the ECHR (*Mabon* 2005). It has been argued that the judiciary could develop this right further based on empirical evidence that shows that children are more capable of understanding the implications of what they are deciding than is traditionally understood (Hagger 2009, Chapter 2). This, and the fact that international trajectories of children's rights seek to develop their autonomous interests (*ibid*) suggest to us that the Regulations should be amended to allow competent children the right to consent to research, not merely the right to assent as suggested by Cave (2010). In practice and in accordance with ethical guidelines, a child's assent *may* be sought where they have capacity as assessed by a broad range of factors (European Commission, 2008). In our view, this is the minimum that should be required rather than a mere consideration of the child's wishes with regards to the research that is required once capacity-appropriate information has been provided.

Whilst we would advocate the right of every child to participate in the decision-making process, to receive appropriately designed information and to be respected in the light of their burgeoning autonomy, we also accept that parental authority will carry the greatest weight and the law does not *require* parents to involve their children in making decisions. In light of this, it is important to explore the role of TM and parental consent to paediatric research specifically. Before we do so, the ethical concerns about TM need to be examined in more detail as the law only provides a framework within which to view TM, and an incomplete and uncertain one at that.

Does TM Matter?

Recognition that TM is potentially at play in the research context serves as a warning that informed consent, designed to protect human participants in research, may not fulfil its

intended object when it is in place merely as a bureaucratic function. This is because the bureaucratic procedure may be fulfilled without the person gaining consent employing measures to check understanding, explore possible misconceptions, and ensure all those involved, parents and child for example, have been involved in the process to an appropriate degree. The free and informed consent of the competent participant in clinical research, (or their parent/ legal representative in the case of children and incompetent adults), is not only a legal necessity as is described above but also a moral requisite. It is set out in many ethical codes such as the Nuremberg Code (Allied Control Council, 1949), the Declaration of Helsinki (WMA, 2008) and the Belmont Report (National Commission, 1976). The right to physical and mental integrity of the person under Article 3 of the European Union Charter of Fundamental Rights has particular relevance. It notes that, in the fields of medicine and biology, the free and informed consent of the person concerned must be respected (EU Charter of Fundamental Rights, 2000). The reasoning underpinning these codes has recognised the importance of respect for persons.

The weaknesses of informed consent are well-documented (O'Neill, 2002 and Mason and O'Neill, 2007) , but a *gross* misconception about the main purpose of a study, its risks and benefits must be regarded as significant, since if consent has any value it is as an expression of respect for persons and is not merely a permissive nod. Whilst it may be true that the context of contemporary paediatric research is a long way from the atrocities of the infection studies conducted on children at Willowbrook (Edsall, 1971 and Goldby, 1971), this does not mean that we can afford to weaken contemporary ethical standards. Recent controversies show there is good reason to remain concerned about the potential harms which may arise in the research context. We need regulation of paediatric research because unethical research has continued to be discovered. For example, in 2000, it was alleged that

research was carried out on premature babies at North Staffordshire Hospitals without parental consent about a decade previously (Smith, 2000 and NHS Executive, 2003). Fortunately, now, controls are such that no REC would approve such trials in the UK thus effectively precluding them from taking place. Yet, ethical and legal principles have struggled to keep pace with scientific developments and this has been particularly evident where biotechnological advances are concerned (Buxton, 2007).

The question as to whether the TM really matters might well be posed where participation in a scientifically sound study in which participants are not disadvantaged by their participation (Miller and Joffe, 2006). However, we suggest that TM does matter because having a well-designed and ethically robust study only speaks in favour of a researcher being justified in approaching a potential participant and not to enter participants irrespective of their understanding the study or not. What remains to be addressed in the recruitment process are some of *the* central ethical issues within medical research, what might be broadly called ‘respect for persons’ but taken to include a regard for the vulnerability of the participant and respect for their autonomy. Thus the responsibilities and duties of the researcher extend beyond the design and ethical justification of the research to the means by which respect for persons is best demonstrated. Where parental consent is required for a child’s participation in research, then respect for persons requires that the autonomy interests of the parents are respected alongside a balanced consideration of the child’s best interests and respect for their burgeoning autonomy.

Following what has been described as the ‘strong model’ of informed consent (Meisel, Roth and Lidz, 1977), a researcher may fail in their duty of care when they do not attempt to provide information appropriate to patient/parent’s needs, in its substantive

content or in its mode of delivery thus impeding the exercise of autonomy of the participant. Autonomy is also at stake when the participant lacks the competency to understand the necessary information about the study and the researcher may be regarded as culpable if they fail to properly assess the participant's understanding. Even if no harm comes to the participant in an otherwise scientifically robust and ethical study there is still reason to believe that the dignitary harm against the person is significant and ought to be avoided (Dresser, 2002, Appelbaum and Lidz, 2006). Although the strong model has been criticised for taking a too rationalistic approach, Lidz (2006) argues that nevertheless it remains an important model of informed consent, a claim which seems to be borne out by the accounts of consent evident in UK law set out earlier.

A second set of concerns revolve around broadly consequentialist considerations with an emphasis on the potential beneficial consequences of well designed and executed research. Several commentators have started to challenge the 'disadvantage thesis': the presumption that participation in a clinical trial necessarily disadvantages participants (Miller and Joffe, 2006 and Saver, 2006). The implication of this approach is that it threatens a reversal of the traditional stance enshrined in the Declaration of Helsinki that the interests of the research subject are above all other the interests (WMA, 2008). If it is often difficult to meet the 'informed' standard of consent, then should consent be a lesser concern where there are other safeguards in place? For example when a study is well designed and has been subject to rigorous peer review and ethical approval? There may be some support for this view in the light of the special procedure in place for recruiting into time critical or emergency research where a participant lacks capacity to consent and there is no time to consult others. However, the prospect of extending the approach adopted in emergency research to persons who have capacity would be disproportionate and wrong. As Appelbaum and Lidz (2006) and others

(Dresser 2002, Lidz 2006) have argued, although the concept of informed consent is problematic, the overriding concern in the research context should be the principle of respect for autonomy and the willing, informed participation of the recruited individual. These commentators argue that, whilst it may be a justifiable act of beneficence to restrict, or indeed circumvent autonomy when the restriction is to the direct benefit of that individual, this ought never to be the case in research where the participants' role in the research is to promote the interests of others, including the researcher and wider society. We concur with the view that this would constitute a form of wrongful instrumentalisation of the person. As Appelbaum and Lidz (2006) argue, we should not be willing to accept a compromise when effective mechanisms for mitigating the problem may exist.

So far we have indicated some of the broad problems associated with the TM but there is a further tier of complexity when it is a parent consenting for their child.

TM and Parental Consent for Children

Shilling and Young (2009) in a review of the literature dealing with parent's experiences of providing consent to clinical trials identify a number of factors that influence the complexity of the consent process. Parents are particularly vulnerable if the request to consent to research comes close to the diagnosis of a serious condition, or where the condition in question is acute and potentially life-threatening. In comparison to parents of children with less serious chronic conditions, parents of more acutely ill children recognised that their decision-making ability was impaired, sometimes regretted their decision and sometimes failed to recognise the voluntary nature of research. Shilling and Young also report several studies where, as a result of participating in randomised trials, parents felt disappointed, let

down and even expressed concerns that their child had been discriminated against when they ‘failed’ to be allocated to the experimental arm of the study, thus suggesting a lack of understanding about the nature of randomisation. More relevant to this paper is their report of studies where parents of very sick neonates and children with cancer state a greater acceptance of risk in the hope of a cure. In addition, several parents reported a feeling of pressure to participate in Phase I studies so as not to be seen as ‘giving up’ on their child.

One must be cautious not to generalize these findings to all parents faced with the decision to put their child into a trial. Research is beginning to uncover some of the significant cultural, social and economic factors which may indicate the important influences for certain groups of parents (Shilling and Young, 2009). Moreover, the situations in which parents have to make such decisions are not homogenous. Parents of children with neuromuscular disorders (NMD) are not in the same position as parents with very sick neonates or children with cancer. Thus more empirical work is needed to understand the significance of these different circumstances. As we have described elsewhere (Woods and McCormack, in press), NMDs are represented by quite powerful parent and patient organizations who actively lobby for research, generate funds to support research and establish research registries and bio-banks. Involvement in parent/patient organizations comes with an expectation that research will happen and that members will put their children forward for inclusion. It is in the context of working with such organizations that we have recognised many of the factors which may easily contribute to a form of the ‘collective therapeutic misconception’ described above. In a context in which there are currently no curative treatments for these conditions, it is very easy psychologically to render research as synonymous with treatment and for parent/patient activists to not only expect research to take place but to expect that they or their child should be included in such research (ibid.).

Discussion

Ethical guidance and legal directives share a consensus that consent to research ought to be given by a competent participant (or their proxy), be free and informed. However, despite the consensus on the principle, the challenge of determining when the ‘free’ and ‘informed’ conditions have in fact been met. In theory, the formula for informed consent follows the form that certain things should be known and understood by the person consenting (the epistemic conditions), that they should be in a certain state with regard to their volition (the liberty conditions), and that they ought to be able to rationalise their decision by weighing the information about risks and benefits (the cognitive conditions). The formula does not leave room for other factors such as the possible false or irrational beliefs held in parallel by the individual, or the role that hope may play in the interpretation of facts and reasons. These other factors grow in significance when the person consenting is not the person who will be the bearer of the risk such as when parents are consenting for their child. It is easy to empathise with the mother, who desperate to do everything possible for her gravely sick child, will externally conform to the model of informed consent whilst internally disregarding the niceties of trial design, and the theoretical risks, in order to get their child into a study conducted by a world leading researcher (Henderson, 2008). Could what we have described be justifiably regarded as an invalid consent if the mother is not in that particular state of grace in which she meets the epistemic, liberty and cognitive conditions? This may be the case, even though the process may have met the legal and regulatory requirements in that the parent is seemingly free from *external* coercion and comprehensive information has been provided regarding the purpose and risks of the trial. There is a real paradox here and not simply an academic point. If a valid consent requires that the person consenting meets certain conditions, voluntariness and freedom from relevant constraints, appropriately

informed, and able to use this information so as to weigh the risks and benefits of participation, then it matters that each component is satisfied to the relevant degree.

As we have seen, the consent process must be adequate to the task of ensuring that these requirements are satisfied. Provided there is evidence that these issues have been explored and understood using best endeavours, there is likely to be legal compliance. To attempt an examination of a participant's motives, or those of their proxy, could even be seen as overly paternalistic and intrusive. The law reflects the value placed on the ability to freely choose actions from options which are fully understood: to do so is to recognise the necessary freedom for an individual to 'make her life her own' (Harris 2003, p. 10), particularly with respect to medical decision-making (*Re B* 2002, para 20). To scrutinize personal reasons for decision-making could also be seen as an invasion of privacy and a potential breach of the right to private and family life under Article 8(1) of the European Convention on Human Rights enshrined in England in the Human Rights Act 1998. This Article has been interpreted broadly including 'the physical and psychological integrity of a person' (*Pretty*, 2002).

The consent process must be adequate to two thresholds, it must enable the person consenting to consent or refuse to consent without prejudice and, it must also allow the researcher to exercise some judgment as to whether the conditions for a valid consent have been satisfied. A researcher from within the TREAT-NMD consortium provided the following example. The context was a phase I clinical trial of a novel 'anti-sense' drug with potential therapeutic use in DMD. The study involved injection into a single muscle followed by a biopsy of the muscle after a period of time for the agent to have an effect. There was no possibility of direct benefit to the subject. However during the consent process the researcher asked the parents of the eligible child to repeat their understanding of the

purpose of the trial. In their response the parents insisted that the trial would help their child to walk again. Eventually the researcher decided that the child should not be entered into the study because he judged that the parents were unable to give a valid consent (Anonymous personal communication, 2009).

It may be unfortunate that these parents voiced with particular force what many others also express, namely the hope that their child will benefit. It would be hasty to draw the conclusion from such examples that parents who express this kind of hope are likely to be rendered incompetent in such circumstances and therefore should not be judged unable to consent for their children. The issue of hope and its relevance to consent was the focus of some eloquent discussion by parent delegates during a debate on TM held at an international conference hosted by TREAT-NMD in Brussels (2009). The question was put that if hope is seen as problematic in the research context then this would disqualify most parents from consenting for their children unless, *per impossible*, it was feasible to determine a threshold for hope that was compatible with a valid consent.

Hope and Misconception

In our work with researchers and patient organizations in which we have explored the challenge of consent and TM, it has become apparent that in discussing hope as a possible factor within TM there is the potential for parents to believe that they are being either denied hope or else denied the capacity to consent for their children. If true, both would seem wrong. Hope is a complex concept but there is a consensus that hope has a role in helping individuals to cope with existential challenges, including the ability of a parent to cope with their child's life limiting disease (Samson et al, 2009). Hope is a leitmotif in the discourse we have

witnessed when parents and patients meet or communicate virtually through the various media supported by patient organizations. Certainly there should be more empirical work conducted in order to understand the dynamics of hope and to examine whether the coping that hope engenders can be directly constructed through the support and information available to parents (ibid.). Where hope seems problematic is when it takes the form of a kind of self-deception, though we raise this point with a certain degree of caution. We suspect that many parents go through a phase of hoping for a quick fix medical cure for their child's condition. However, where this form of hope becomes the motive for entering their child into a study then it has the potential to feed a serious misconception. As we have observed elsewhere (Woods and McCormack, in press)) this form of blind hope does motivate parents to take extraordinary measures in order to try and ensure a place for their child in a clinical trial. We suggest that this form of blind hope, perhaps 'blind optimism' would be more accurate, ought to be distinguished from the form of hope that results in a disposition not to despair and thus acts as a means of coping. Horng and Grady (2003) capture this as a distinction between therapeutic misconception/mis-estimation which may distort capacity to consent and therapeutic optimism which is always tolerable because it does not compromise autonomy.

The French existentialist philosopher Marcel (1995) gives an account of hope that is directly relevant to this context. Marcel draws a distinction between two realms: that of fear and desire on the one hand, and despair and hope on the other. Optimism he argues, belongs to the realm of fear and desire because it imagines and anticipates a beneficial outcome. Treanor describes the contrast: '[o]ptimism exists in the domain of fear and desire. However, the essence of hope is not 'to hope that X', but merely 'to hope.... The person who hopes does not accept the current situation as final; however, neither does she imagine or anticipate the circumstance that would deliver her from her plight, rather she merely hopes for

deliverance. The more hope transcends any anticipation of the form that deliverance would take, the less it is open to the objection that, in many cases, the hoped-for deliverance does not take place. If I desire that my disease be cured by a given surgical procedure, it is very possible that my desire might be thwarted. However, if I simply maintain myself in hope, no specific event (or absence of event) need shake me from this hope. (2010, p. 14)

This distinction has some resonance with the, albeit limited, empirical work conducted in this field. Samson et al 2009 in their work with parents of children with DMD describe a shift in parental hope from the concrete and specific to a ‘spiritual and intangible form... an inner resource that can help sustain parents’ efforts in caring for their sick child’ (p. 112). Jansen (2006, 2011) also points to the possibility that ‘therapeutic optimism’ may not be incompatible with a valid informed consent to research. In raising concerns about the quality of parental consent for research we are concerned not to diminish the importance of this sustaining form of hope but rather to identify the potential that a blind optimism may have in contributing to an abiding and serious TM.

Conclusion

We believe that there is an important agenda for further empirical research into the role of TM in consenting to research with children. In particular, the relationship between hope and TM in the context of parental consent for research is likely to contribute to the quality of informed consent and reassure researchers, parents and regulators alike. There are also supplementary strategies which can be adopted *now* in order to improve the quality of informed consent to research. (Horng and Grady 2003, and Jansen, 2011). A different attitude towards the relationship between research regulators, researchers and research

participants needs to be fostered, one which seeks to diminish the power differences that continue to exist in the research context. We have argued elsewhere that a closer relationship between patients, patient organizations and researchers up-streaming the involvement of patients in the research design process is likely to lead to a better understanding of research by patients, and a greater understanding of the needs and interests of patients by researchers (Woods and McCormack in press). In the final analysis however, it is the researcher's responsibility to ensure that adequate procedures for informed consent are in place and that these are satisfied through their best endeavours before a child or any other individual is entered into a clinical trial where such consent is required. To expect more is not only unrealistic but neither morally nor legally required; it may even risk an invasion of privacy of the individual consenting, a right that has been recognised as deserving the strongest legal protection.

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