"Fortunate are those who Take the First Steps"?

The Psychosocial Impact of Novel Drug Development

Rebecca Dobra[1,2,3] Susan Madge[1], Isaac Martin[3], Paul Weldon[4], Nicholas Simmonds[1,3], Jane C Davies[2,3]

1 Department of Cystic Fibrosis, Royal Brompton Hospital, London, UK

2 Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, London, UK

3National Heart and Lung Institute, Imperial College, London, UK

4 Department of Psychological Medicine, Royal Brompton Hospital, London, UK

Corresponding author, Rebecca Dobra r.dobra@rbht.nhs.uk

Key Words

Clinical trials; Clinical research; Drug development; Psychosocial impact

Abstract

Novel drug development offers people with cystic fibrosis exciting opportunities but is not without challenges. Currently, there is an understandable emphasis on protecting patients' physical health when developing treatments. However, there appears to be little consideration of how novel drug development impacts on psychosocial wellbeing, or the downstream consequences of this.

Using an illustrative case and reviewing the literature we explore themes regarding the psychosocial impact of trial participation and novel drug development and identify areas requiring further research. Through this, we hope to prepare healthcare professionals to better understand the needs of their patients in this rapidly evolving landscape.

Background

Drug development pipeline expansion and the advent of novel cystic fibrosis transmembrane conductance regulator (CFTR) 'modulator' drugs present people with cystic fibrosis (CF) substantial hope for improved quality of life and life expectancy[1,2]. There are more than 100 drugs in development, and the number of trials conducted is increasing each year[1]. Healthcare professionals (HCPs) will increasingly encounter patients who are considering trial participation, actively participating in trials or have recently completed a trial. Patients in clinic are hoping for a shift in available treatment options in the near future.

In general, this paradigm brings exciting opportunities. However, it also presents new challenges. There is currently a vital emphasis on maintaining patients' physical safety whilst developing new therapies. However novel drug development carries an emotional impact, not limited to patients who are currently participating in trials[3–5]. Such impacts may have downstream consequences, conceivably influencing health perception, quality of life, mood and engagement with clinical care. To date, these important issues have received minimal consideration.

Here, we share the experiences of a patient to introduce some emotional challenges of novel drug development. We then review the literature pertaining to the psychosocial impact of trial participation and novel drug development, which exist predominantly within oncology[3]. Through identifying and exploring these themes we hope to provide a framework to better prepare HCPs to anticipate and meet the needs of their patients in this evolving CF landscape.

Illustrative Case

A 37-year-old female with CF (F508 homozygous), pancreatic insufficiency and CF related diabetes enrolled in a placebo-controlled trial of a modulator drug in February 2016, later entering an open-label phase. Her baseline forced expiratory volume in the first second (FEV_1) was 60%, with a body mass index (BMI) of 19.5 and HbA1c of 7.2. She works fulltime and has an excellent social support

network. Whilst on the trial she reported significant symptomatic improvement, particularly improved energy levels, reduced exacerbation rate and her FEV_1 remained stable. The physical and psychological wellbeing attributed to the trial drug kindled a desire to have a baby.

She discussed this with trial and clinical teams. There were no contraindications to pregnancy, and standard CF advice was given with particular attention on increasing her BMI. Trial protocol would have meant withdrawing from the trial, and continuing contraception for 90 days prior to attempting to conceive. Outside the trial, there was no mechanism for her to continue to receive modulator therapy.

Making this decision raised anxieties around the impact on her long-term health and short-term ability to carry a child. She acknowledged that the drug was investigational, but wrestled with a perceived injustice of being unable to restart the trial drug following the birth of her child, fearing this had the potential to shorten her life expectancy and deny her the opportunity to see the child grow to maturity. She resented that, had her health deteriorated during the washout period, she would not have had the option to restart the drug and delay plans to have a baby. She was frustrated that the trial was unable to provide the same collaborative flexibility as her clinical team. Despite reassurance, she felt guilt about withdrawing from the trial, fearing she was letting down the team or would be judged for wasting an opportunity unavailable to her CF peers.

Review

The body of literature pertaining to the psychosocial issues of trial participation focusses on cancer trials[3]. This has some generalizability although the heterogeneity of prognosis, treatment options available and structure of care provision make some findings poorly transferable to a predominantly young population with chronic diseases such as CF. Here, we highlight the most relevant findings and consider how they might relate to the CF population. The psychosocial and biological impacts of novel

drug development are almost inseparably interwoven. As such a review of purely the emotional issues cannot exist in isolation. However, we try to bring the psychosocial issues to the foreground.

Before trial enrollment

The majority of patients expend substantial time and energy considering participation[6,7]. Patients describe fears about the risks of participation, anxiety about financial cost of participation and concern about the effect on day-to-day lives[6,8,9].

Having decided to participate, some patients describe a sense of personal failure if they don't meet entry criteria or "screen-fail"[10]. A problem particularly relevant to CF is the risk of exacerbation between screening and randomisation visits. We are aware of anecdotal reports of patients going to extreme lengths to minimise their risk of exacerbation during this critical period, impacting on their psychosocial well-being.

During the trial

During the trial, patients may experience anxiety about side effects and risk of allergy[3,5,10,11]. Whilst some patients may feel better secondary to the intervention, some describe increased symptomatic awareness which may be due to regularly considering adverse events or completing symptom diaries[12]. A group of patients with chronic obstructive pulmonary disease (COPD described becoming upset when regularly seeing objective measures of their health when participating in a trial[10]. This may be less relevant to a CF population who regularly see their lung function in clinic, but trial participation may still bring objective measures to the forefront of their thoughts. Trial participation may allow illness to play an augmented role in patients' lives[10] potentially altering their perception of health and self.

Uncertainty about randomisation can cause patients unease, and many patients find it disconcerting not knowing if they are on placebo or active drug[4,13]. Procedures such as biopsies and even blood sampling cause participants distress. Adequate anaesthetic/analgesia and good explanation only partially alleviates this distress[3,10].

During trial participation daily lives such as work, family commitments and education are impacted, particularly with early phase trials. The time commitment is consistently cited as one of the hardest parts of trial participation across all disease groups[3–6,10]. This effect may be more pronounced in our young patient group with busier lives. As in this case, protocol inflexibility may be a major source of frustration to patients, even if they can, on one level, understand the drivers. Many elements contribute to this phenomenon including tight visit windows, rigid rules about drug interruption and prohibited concomitant medications.

After trial participation

Arguably it is the post trials experience that has the potential to cause the most significant and lasting consequences of trial participation.

On trial completion, patients may experience a loss of hope if the intervention has proved unsuccessful either at a personal or trial level[10]. This loss of hope may impact mood and health perception. Patients may experience anxiety about stopping a drug if they have found it beneficial. Even with open-label phases or managed access programmes uncertainty about funding causes worry. Patients who complete earlier phase trials do not have these options and some fear deterioration on stopping therapy. Anecdotally some patients describe altered health perception when stopping trial therapies that have alleviated symptoms as the contrast becomes clear.

In the rare case that trials are terminated because of safety concerns this can be unsurprisingly accompanied by anxiety, but also potentially anger towards the wider team for suggesting participation[14]. If a trial fails, patients may feel despondent that their participation has been "pointless". As in the case we described, participants may experience guilt if they decide to withdraw from trials, feeling they are letting down the team, or wasting a desirable opportunity[14,15].

Paediatric Specific Considerations

Drugs in children have different pharmacokinetics and pharmacodynamics. As such drugs must undergo testing in appropriate age groups to confirm safety and, many would argue, efficacy[16]. Trial participation for children undoubtedly brings its own challenges.

Although assent is required from children in trials, this can be difficult to establish practicably. Therefore, parents take much of the burden of the consent process[16]. Parental guilt is a major theme running through the literature[17]. Parents feel guilty that they may be making the wrong decision, particularly for very young children who are essentially unable to contribute to the assent process. Parents perceive children as more vulnerable and at greater risk from trial participation, causing heightened anxiety and contributing to feelings of guilt[18].

Children experience significant distress surrounding blood tests[16,18], frequently cited as a reason for withdrawal from paediatric trials[16]. Some parents express concerns that blood sampling as part of trial participation may increase apprehension regarding blood sampling in a clinical context. Whilst this may occur, we have also observed the converse, with a sustained improvement in anxiety levels as procedures become more routine.

The psychosocial consequences of children participating in trials has bearing on the wider family. Parents express concern that siblings may lose out on opportunities or experience jealousy of the

attention the participating child receives. Although only one parent is required to consent to trial participation, disagreement between parents can be complex to resolve[19]. There are additional challenges if families have two or more children with CF and only one is eligible to participate.

Novel Drug Development in Context

It is important to emphasise that novel drug development has emotional implications reaching far beyond those who actively participate in trials.

Patients who choose not to participate in trials may feel conflicted in this decision for numerous reasons. Within cancer trials, many patients say they feel a moral duty to enroll, and feel guilty for choosing not to participate[20]. Before deciding to decline trial participation, patients may spend a lot of time considering the risks vs benefits[6], and the angst this can cause should not be underestimated. Within the CF trials space we suggest this guilt and anxiety may be accentuated by feeling they are turning down an opportunity unavailable to others with CF.

Furthermore, not all patients who wish to participate in trials have the opportunity to do so. Trials networks have been set up to improve access to CF trials, but there are many other reasons patients may not be able to participate. For example, some patients may not meet the eligibility criteria, leading to frustration and disappointment[10]. Another emergent challenge is competitive trial recruitment. When patients do not get places on oversubscribed trials they can experience a range of reactions including a loss of hope or anger, potentially influencing their perception of health and clinical care. Such trials present important questions of how we select to trials and how we manage the distress of those who do not get places.

As new drugs become available through clinic, we must consider the loss of hope if the novel therapies prove ineffective for individuals, and even the loss of identity if they prove highly effective[18].

Finally, in a time of genotype specific modulators and reimbursement concerns many patients fear delays accessing effective drugs, or that modulators may not be developed for their genotype. This may cause resentment and frustration towards sponsors and regulating bodies, increase anxiety about current and future health status and contribute to dissatisfaction with current treatment regimen.

Conclusions

Novel drug development presents patients with exciting opportunities. However, it is accompanied by its own challenges, with potential downstream consequences for patients' psychosocial wellbeing. This area requires further consideration, and prospective research, particularly within CF where the trial pipeline is expanding rapidly. Through our case and review of the literature, we are able to identify and explore some of these themes. However, it is without doubt that new challenges will emerge as the landscape evolves. As ever, we must take an adaptive, multidisciplinary approach to support patients through these challenges with sensitivity. We must ensure that patients' emotional needs are met before, during and after trial participation and be aware of the challenges that clinic patients will encounter in this changing treatment paradigm.

Declaration of Interests

RD, SM, IM and PW have no interests to declare. NJS has consulted for Vertex Pharmaceuticals, Chiesi, Roche, Pulmocide, PTC Therapeutics and Gilead. JCD has served on advisory boards and participated in clinical trial leadership, educational activities and grant review board activities for a number of pharma companies active in CF clinical trials: Vertex, PTI, Galapagos, AbbVie, AlgiPharma, Chiesi, Enterprise, Teva, Ionis, Eloxx, Roche, Gilead

Acknowledgements

With many thanks to the patient whose case we describe for allowing us to share her experiences.

Bibliography

[1] Mayer-Hamblett N, Boyle M, VanDevanter D. Advancing clinical development pathways for new CFTR modulators in cystic fibrosis. Thorax 2016;71:454–61. doi:10.1136/thoraxjnl-2015-208123.

[2] De Boeck K, Bulteel V, Tiddens H, Wagner T, Fajac I, Conway S, et al. Guideline on the design and conduct of cystic fibrosis clinical trials: The European Cystic Fibrosis Societyâ€“Clinical Trials Network (ECFS-CTN). J Cyst Fibros 2011;10:67–74. doi:10.1016/S1569-1993(11)60010-6.

[3] Walsh E, Sheridan A. Factors affecting patient participation in clinical trials in Ireland: A narrative review. Contemp Clin Trials Commun 2016;3:23–31. doi:10.1016/j.conctc.2016.01.002.

[4] Mills EJ, Seely D, Rachlis B, Griffith L, Wu P, Wilson K, et al. Barriers to participation in clinical trials of cancer: a meta-analysis and systematic review of patient-reported factors. Lancet Oncol 2006;7:141–8. doi:10.1016/S1470-2045(06)70576-9.

[5] Fayter D, McDaid C, Ritchie G, Stirk L, Eastwood A. Systematic review of barriers, modifiers and benefits involved in participation in cancer clinical trials 2006.

[6] Kurt A, Kincaid HM, Curtis C, Semler L, Meyers M, Johnson M, et al. Factors Influencing Participation in Clinical Trials: Emergency Medicine vs. Other Specialties. West J Emerg Med 2017;18:846–55. doi:10.5811/westjem.2017.5.33827.

[7] Cassileth BR, Zupkis R V., Sutton-Smith K, March V. Informed Consent — Why Are Its Goals Imperfectly Realized? N Engl J Med 1980;302:896–900. doi:10.1056/NEJM198004173021605.

[8] Mahmud A, Zalay O, Springer A, Arts K, Eisenhauer E. Barriers to participation in clinical trials: a physician survey. Curr Oncol 2018;25:119–25. doi:10.3747/co.25.3857.

[9] Unger JM, Cook E, Tai E, Bleyer A. The Role of Clinical Trial Participation in Cancer Research: Barriers, Evidence, and Strategies. Am Soc Clin Oncol Educ Book Am Soc Clin Oncol Meet 2016;35:185–98. doi:10.14694/EDBK_156686.

[10] Dobra R, Guilmant E, Higgins T, Fleming S. Understanding and improving participants' experience of health research; Patient evaluation of research participation in a dedicated respiratory biomedical reserach unit (BRU) Clinical resreach facility (CRF). Thorax, Br. Thorac. Soc. Winter Meet. Queen Elizab. II Cent. Broad Sanctuary Westminster London SW1P 3EE 2 to 4 December 2015 Program. Abstr., 2017, p. ; Vol 70; Suppl 3.

[11] Lawton J, Snowdon C, Morrow S, Norman JE, Denison FC, Hallowell N. Recruiting and consenting into a peripartum trial in an emergency setting: a qualitative study of the experiences and views of women and healthcare professionals. Trials 2016;17:195. doi:10.1186/s13063-016-1323-3.

[12] Kerrison S, Laws S, Cane M, Thompson A. The patient's experience of being a human subject. J R Soc Med 2008;101:416–22. doi:10.1258/jrsm.2007.070288.

[13] Featherstone K, Donovan JL. Random allocation or allocation at random? Patients' perspectives of participation in a randomised controlled trial n.d.

[14] Lawton J, White D, Rankin D, Elliott J, Taylor C, Cooper C, et al. Staff experiences of closing out a clinical trial involving withdrawal of treatment: qualitative study. Trials 2017;18:61. doi:10.1186/s13063-017-1813-y.

[15] Morris N, Bàlmer B. Volunteer human subjects' understandings of their participation in a biomedical research experiment. Soc Sci Med 2006;62:998–1008. doi:10.1016/j.socscimed.2005.06.044.

[16] ECFS. The early Cystic fibrosis years. 1st ed. 2018. Chapter 16 De Boeck, van Koningsbruggen-Rietschel Safe Ethical Clinical Trials in Pre-School Children with CF Pages 265-274.

[17] Shilling V, Young B. How do parents experience being asked to enter a child in a randomised controlled trial? BMC Med Ethics 2009;10:1. doi:10.1186/1472-6939-10-1.

[18] Joseph PD, Craig JC, Caldwell PHY. Clinical trials in children. Br J Clin Pharmacol 2015;79:357–69. doi:10.1111/bcp.12305.

[19] Broome ME, Richards DJ. The influence of relationships on children's and adolescents'

participation in research. Nurs Res n.d.;52:191–7.

[20] Madsen SM, Mirza MR, Holm S, Hilsted KL, Kampmann K, Riis P. Attitudes towards clinical research amongst participants and nonparticipants. J Intern Med 2002;251:156–68.