PhD Project Proposal - N of 1 trials and the individualization of drug treatments

1. Background to the study

It is widely recommended that appropriate pharmacological treatments are both evidence based (Sackett 1996) and individualised (Department of Health 2010). This requires input from doctors (to prescribe appropriate drugs) and patients (to use the drugs appropriately). In order to achieve appropriate treatments, patients and healthcare providers must work together to facilitate a diagnosis and the identification of appropriate treatments. If necessary, drug treatments are prescribed by a health professional, and (unless they are in hospital) the patient uses the drug outside the healthcare system. However, supporting patients to use drug treatments in the context of their own lives is not simple. Adherence, (that is 'the extent to which the patient's behaviour matches agreed recommendations from the prescriber'; Horne et al 2005) to prescribed medication is low (DiMatteo 2004), and interventions designed to increase adherence by educating or increasing patients' motivation have limited success (Haynes 2008). As adherence may actually increase side-effects, it is necessary that patients are supported to manage their own treatments. For example, some medications may have more side-effects if they are not taken consistently.

Pound et al (2005) provided evidence to suggest that, outside the consultation, many patients were already individualising their treatment. In a synthesis of qualitative studies of medication taking, Pound et al (2005) suggested that patients' use of medication was influenced by a number of factors, including judgments about the relative risks and benefits of using medications, the likelihood and impact of adverse effects, the acceptability of the treatment regime in their lives, and the influence of significant others. Patients were often motivated to minimise their use of medication whilst still achieving some gain, to make the regime better suited to their lifestyle or more cost effective. Patients actively sought answers to questions they had about their medication - what happens if the medication is not taken, or is taken at a lower dose; how low a dose would still be effective; could non-pharmacological treatments be more effective; is the medication working; is the medication interfering with daily life. In an attempt to answer these questions, patients modified their treatment regimens by stopping or lowering the dose of medication to test its effectiveness (lay testing); only taking medication when symptomatic (symptomatic use of medication); only taking medication or taking more medication to offset lifestyle factors such as drinking alcohol (strategic use of medication) and replacement of medication with non-pharmacological treatments. Patients may also modify their treatment regimens by increasing the dose of medication, in order to achieve a larger effect (e.g. for medications to treat painful conditions), and by mixing prescribed and non-prescribed pharmacological treatments (e.g. in an attempt to achieve greater pain relief). Thus many patients are individualising their own drug treatments according to their own criteria, often without the support of their healthcare provider. Sub-optimal use of the available evidence to support and optimise these practices may lead to a focus on the pathology of a chronic condition, rather than the burden of treatment which, in turn, may lead to non-adherence, resource waste and poor outcomes (May et al, 2009).

N of 1 trials

N of 1 trials (or single subject clinical trials where a single patient is randomised to a crossover comparison design treatment) consider an individual patient as the sole unit of investigation in a study which investigates the efficacy or side effects of a treatment (Lillie et al 2011). N of 1 trials (also described as individualised medication effectiveness tests, Nikles 2005), involve monitoring, reviewing and adjusting treatments in order to identify the best treatment for an individual (Guyatt 1986). N of 1 trials aim to provide evidence based information on individuals (as opposed to a population average), and are considered to be the ultimate method for individualising treatment (Guyatt 1986; Lillie 2011; Nikles 2005a). Rigorously conducted N of 1 trials involve randomisation, blinding, and objective monitoring of outcomes. They have been defined by Guyatt as 'randomised, double blinded, multiple crossover comparisons of an active drug against a placebo or an alternative treatment in a single patient' (Guyatt 1986). More pragmatic N of 1 trials, used to inform clinical practice, would require healthcare providers and patients identifying

and testing a specific dose or treatment, monitoring the impact on their condition, making adjustments to the regimen and evaluating further.

N of 1 trials are a research method traditionally used to compare the effectiveness of two (or more) interventions, for example two drug treatments. In this case, the intervention is the drug(s), and the N of 1 trial is the trial design. However, N of 1 trials can also be considered to be interventions in themselves. Randomised trials of (formal) N of 1 trials versus standard care have been conducted, and suggest that N of 1 trials can lead to a reduction in medication use without increasing symptoms (Mahon 1996).

2. <u>Problem or issue to be investigated</u>

While research has been undertaken to establish N of 1 as a *methodology* (e.g. whether or not treatment changes result from a patient participating in an N of 1 trial), little or no work has established the role of N of 1 as an *intervention* (e.g. if participation in an N of 1 studies helps or hinders an individual to find a treatment that works best for them).

Mahon et al (1996) conducted a study with 31 patients, in which N of 1 trials were compared with standard practice for patients with irreversible chronic airflow limitation. 15 patients received standard practice (whereby theophylline was stopped and resumed if their dyspnoea (breathing problems) worsened); while 16 patients were randomised to a single patient randomised crossover comparison (N of 1 study) of theophylline against placebo. After 6 months 47% fewer N of 1 trial patients than standard practice patients were taking theophylline, without adverse effects on either exercise capacity or quality of life. However, when the study was replicated in a larger group of patients (Mahon et al 1999) no such improvement in exercise capacity or quality of life was reported, although the authors suggest that the research was conducted suboptimally (e.g. patients had fewer treatment periods than the original research).

In this study we propose to conduct a review to establish whether N of 1 trials can effectively be used to achieve an individualised treatment strategy for an individual patient. We are not concerned with the *effectiveness* of the two (or more) drug treatments that are being compared; rather, we are interested in whether the *process* of taking part in an N of 1 trial is effective in helping the patient to identify an individualised drug treatment strategy. For example, an N of 1 trial will provide a mean score (on a specific outcome) for each drug treatment for each individual patient. From this, we can see how effective each drug is for each patient. However, the review will investigate whether N of 1 trials are successful in identifying an individualised treatment strategy, and whether the patient's treatment, satisfaction, or knowledge change after the trial. Therefore, whilst the N of 1 trial will be a randomised, double blinded, multiple cross-over comparison of an active drug against a placebo or an alternative treatment in a single patient, the review will essentially be comparing pre and post N of 1 trial data (i.e., a before and after design).

Qualitative studies and N of 1 trials

We are aware of two studies that have used qualitative methods to explore patients' perceptions of N of 1 study methodology. Both Brookes et al (2007) and Kravitz et al (2009) identified that patients understood the basic premise of an N of 1 design. Both studies identified that the notion of risk could prohibit recruitment and participation in the pharmacological comparison, but also identified that this design suited some patients more than others (e.g. those who viewed research favourably, and who were motivated to explore treatment options). Less research has been conducted around patients' experiences of specific N of 1 studies. For example, in an N of 1 study of an intervention designed to target coping in the context of communication breakdown following brain injury, Douglas et al 2014 performed an independent assessment of video-recordings of baseline and intervention sessions, alongside a qualitative investigation of the views of clients and close others. The qualitative research highlighted

important strengths of the intervention, including its focus on strategy development, use of video feedback and community practice (Douglas et al 2014).

We are not aware of any studies that have sought to synthesise the findings of qualitative studies associated with N of 1 studies.

3. Hypothesis, aims and objectives

The aim of the study is to explore the value of N of 1 trials, as clinical interventions in themselves, to facilitate the individualization of drug treatments; in other words, where patients have been encouraged to use the N of 1 approach to individualise their treatment, in appropriate circumstances.

The objectives of the study are:

1) To conduct a systematic review of N of 1 trials to identify outcomes of importance to patients and the impact of the trials on these outcomes;

2) To analyse the quantitative and qualitative research around N of 1 studies, to establish the extent to which N of 1 trials could facilitate the individualisation of medicine management;

3) To synthesise quantitative and qualitative data to identify and report on the outcomes that are important to patients;

4) To design an intervention, and associated outcome measures, to determine the clinical utility of an N of 1 trial.

4. Proposed methodology

In a systematic review of N of 1 trials, Gabler et al (2011) identified 108 N of 1 trials reporting on 2154 participants. These were identified by identifying 'landmark' or key papers and subsequent citations , as well as by hand searching the reference lists of known N of 1 papers. While the majority of papers (82%) use a validated patient reported outcome measure, Gabler et al (2011) did not extract data about patients' perspectives on participating in N of 1 studies, nor did they report on relief of symptoms or behaviour change.

Search Strategy

It is our intention to conduct both quantitative and qualitative syntheses that captures a broader range of outcomes that are important to patients (Objective 1). In a scoping search of key databases (The Cochrane Central Register of Controlled Trails (CENTRAL); MEDLINE (Ovid) 1946 to current; EMBASE (Ovid) 1974 to current; PsychINFO (Ovid) 1806 to current; Web of Science (Thomson Reuters) we have identified 2000+ potential abstracts for review, over 500 of which purport to include qualitative data.

We are also aware that some of the work conducted on the utility of N of 1 studies is in the 'grey literature' (e.g. Horwood 2007), and as such a thorough search of other sources will also be required. Online clinical trials registers, including Controlled Clinical Trials, clinicaltrials.gov, International Clinical Trials Registry Platform (ICTRP) and Trials central and the WHO Clinical Trials Search Portal, and a database of systematic reviews, Epitemonikos, will also be searched. We will search for grey literature in the following sites: UK Department of Health, the World Health Organisation, British Pharmacological Society, American Society for Clinical Pharmacology and Therapeutics, American College of Clinical Pharmacology, U.S. Department of Health and Human Services, Health Canada, and Australian Department of Health and Ageing.

We do not intend to register this review with the Cochrane Collaboration as it is not a conventional effectiveness review. However, using the Cochrane Consumers and Communication Review Group's taxonomy (CCCRG 2012); previously published reviews about enhancing medication adherence(Haynes et al 2008); outcomes of effective medicine use that are important to consumers (Ryan et al 2011); and a protocol for personalised care planning (Coulter et al 2013), we will seek outcomes listed below.

Outcomes

Primary outcomes will measure patients' subjective experiences of individualisation, rather than standardised patient reported outcomes (PROMS):

1. Health care utilisation:

a) Patients' medicine taking: measured by self-report or observation (e.g. medication use drug, dose frequency, etc.), knowledge of chronic condition(s), medication appropriateness, impact of medication use, side-effects, treatment satisfaction, self-management behaviour(s), self-efficacy, confidence, competence, ability to access information and/or support).

b) Progression to use of other interventions, such as hospital admission or surgical intervention

2. Health and wellbeing:

a) Physical health: measured by disease specific self-assessment questionnaires, symptom self-report (e.g. symptom diaries, visual analogue scales for pain), observation (e.g. pain behaviours), or biomarkers (e.g.HbA1c, electrolytes, blood pressure)

b) Psychological health: self-report of mood (e.g. anxiety or depression scales), or other relevant psychological domains (e.g. self-esteem, empowerment, coping), observation of altered behaviours.

c) Psychosocial/general health: patient reported quality of life scales, general wellbeing scales, or reports and observations made by carers and or clinical staff.

Secondary outcomes

1. Experiences of clinical support and/or experiences of communications with healthcare providers: measured by self-report (e.g. help seeking scales) or observation (e.g. frequency and duration of consultation).

2. Adherence to agreed treatment regime: self-reported (e.g. interview, diary or questionnaire) or observation (e.g. change from prescribed drug, dose, frequency).

3. Adverse/unexpected outcomes such as exacerbations of symptoms (e.g. biomarkers or observation), dissatisfaction with treatment (self-reported) or other reported adverse events.

We plan to group time points into short (<3months), medium (3 -12months) and long term (>12months) follow up. Where data were collected at different follow-up periods, we will report results taken at the latest time point. This categorization will be relevant for most chronic conditions including terminal illness where many of the N of 1 studies have been conducted.

Data Extraction

Data extraction will be completed using a modified version of the Consumers and Communication Review Group's Data Extraction Template. During this process, the results of studies will be extracted from included studies by the two reviewers. We will compare data extraction forms completed by each review author and discuss disagreements with reference to the original paper. If an agreement cannot be reached, a third review author will be consulted. Authors of N of 1 studies will be contacted and asked to clarify any ambiguities or provide missing data. If authors are unable to provide relevant information, the trial will be included and any areas of uncertainty (due to missing data or missing details) in the trial reports will be noted. Wherever possible, we will extract:

1. General information about the trial (date, location, publication)

2. Study methods (aims of the study, study design, sampling information, inclusion and exclusion criteria).

3. Participant information (number of participants, characteristics of participants, nature of the condition)

4. Intervention information (content of the intervention, delivery provider, location and frequency of intervention)

5. Outcomes and timing of follow-up assessments

6. We will extract data on the number of treatments being compared, the number of planned cross-overs, treatment length and frequency, washout, primary measurement and frequency, and any change in treatment following the trial.

7. Details of funding sources of studies and declaration of interests of study authors will also be extracted.

Data Analysis

In terms of the quantitative data, meta-analysis will be conducted if two or more N of 1 studies of similar interventions report the same outcome (Objective 2). If meta-analysis is appropriate, we will pool percentages for binary outcomes and (standardised) means or mean changes between pre and post for continuous outcomes. If there are sufficient good quality studies in which patients have been randomised to either N of 1 or a control arm, we will conduct meta analysis in the usual way.

For the qualitative data, we anticipate using meta-ethnography (Noblit et al 1988) as the primary method of synthesis, building on the experience of the supervisory team (Objective 2). A summary text for each paper will be constructed and diagramming or mapping may also help to organise and interpret data in the initial phases. Key themes and concepts extracted from these studies will form the fundamental concepts for the synthesis. Meta-ethnography uses “translation” to understand key concepts across papers in terms of each other (either confirming or contradicting each other). We will attempt to account for differences in accounts based on elements of study design, setting, participants, methodology or any existing theoretical framework. Our analysis will be led by the study findings themselves, but we also anticipate that the papers will be informed by the findings in the quantitative synthesis to assess similarities, links and differences between the two bodies of literature.

If possible, we will synthesise the quantitative and qualitative findings into a coherent whole, using the approach of narrative synthesis (Popay et al, 2006) (Objective 3). We anticipate developing a conceptual model that identifies the outcomes that are important to patients, as well as any relationships between them (e.g. duration of treatment and reduction in symptoms). This will inform the development of a pilot intervention.

Patient and Public Involvement

We will work with the PenCLAHRC PPI team to develop an appropriate PPI strategy for this project. It may mean inviting individual members of PenPIG to join an advisory group to review the project proposal and to contribute to the research over the course of the studentship. We previously worked with a subgroup of PenPIG, the ‘compliance’ group, on the topic of drug licensing (Britten et al, forthcoming) and will explore the possibility of working with interested members of PenPIG in a similar way. If there are insufficient members of PenPIG who wish to contribute, we will recruit patients from our other networks.

Development of a pilot intervention

In the final stage of this study, the findings of the individual studies and the overarching syntheses will inform the development of a pilot intervention (e.g. comparing a group randomised to N of 1 with a control group) (Objective 4). The goal of the intervention will be to assist individuals to find treatments that work best for them. We have the possibility of developing this work with Dr Michael Gibbons at the Royal Devon and Exeter Foundation Trust who is an expert in treating Idiopathic Pulmonary Fibrosis. This is a devastating disease for which new and expensive drugs have been developed, in the absence of much certainty about which patients will benefit from them, or whether side effects outweigh any potential benefits.

Timetable

1. Systematic search for N of 1 trials, and associated qualitative studies. Search criteria will be predefined for N of 1 studies (e.g. ("n of 1" adj3 (trial* or stud*)).tw.; "single participa*" or "single patient*" or "single case*" or "single subject*" or "individual participa*" or "individual patient*" or "individual case*" or "individual subject*") adj3 (trial* or stud* or design*)).tw.) and qualitative methodologies (e.g. qualitative or interview* or survey* or "focus group*".tw.)

2. The quantitative and qualitative evidence will be synthesised separately (using meta-analysis and meta-ethnography, respectively).

3. If possible and appropriate, the quantitative and qualitative syntheses will brought together into a coherent whole, to form an overarching synthesis.

4. We will develop a pilot intervention, which will assist individuals to find treatments that best work for them. The intervention could be applicable to specific chronic diseases, symptoms (such as pain, mobility or sleep) or outcomes (such as optimal medication management, satisfaction).

5. Relevance/significance

The global prevalence of all chronic conditions is increasing, with most occurring in developing countries, and projected to increase substantially over the next few decades (Yach et al 2004). Prescribed medication is often given to older people with multiple chronic conditions based on studies of younger persons without significant co-morbidity who have a life expectancy of several decades. Applying the results and/or the clinical guidelines developed from these studies to co-morbid patients is inappropriate because of higher risk to benefit ratios with increased age, co-morbidity, disability, and number of medications prescribed (Garfinkel et al 2010).

A previous review assessing the effectiveness of interventions for promoting adherence to medication failed to show any sustainable effect of interventions on adherence (Haynes 2008). Other reviews exploring outcomes of effective medicine use that are important to consumers (Ryan 2011), promoting patient centeredness (Dwamena 2012) or shared decision making (Légaré 2010) have also focused on adherence as opposed to achieving individualised treatments. We are interested in how medications can be adapted to suit the patient - both biologically and socially. In this respect, non- adherence may sometimes result in a better treatment regime for the individual patient.

A systematic review of N of 1 trials (Gabler 2011) found that such strategies can be effective for identifying optimal treatments. To our knowledge, this is the first review to explore the effectiveness of N of 1 studies as an intervention for individualising treatments in consideration of patients' existing medication use.

Amidst the current concerns around the use of statins, a physician has called for a database of N of 1 studies and self-reported symptoms, which would allow individuals to make an informed decision about the use of statins (Barer 2014). It is our intention to develop an intervention that would facilitate this level of individualised treatment.

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