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Editorial

Challenges and proposed solutions for formative research to inform systematic intervention development in rare and unstudied conditions: The case example of Xeroderma Pigmentosum

Background

The systematic development of interventions to change health behaviours that are linked to morbidity and mortality is a key priority area for the discipline of health psychology. There is, however, a gap in the provision of interventions to change behaviour and improve health outcomes in rare diseases, although the behaviours (e.g., photoprotection) and outcomes (e.g., avoidance of skin cancer) may not be unique to the disease. A rare disease is one that affects fewer than five individuals per 10,000 in the general population (European Commission, 2008), but some may affect far fewer people. A patient survey revealed that perceived unmet needs included the absence or poor availability of social and psychological support (Rare Disease UK, 2013). A report on adherence in rare diseases further suggested that interventions to improve self-management were needed, and should address perceptual (e.g., the need for treatment, benefits, side effects), psychological (e.g., depression, coping), and practical barriers (e.g., forgetting, routines; Cooper & Clatworthy, 2016). Despite this, a PubMed search of randomized controlled trials (RCTs) of non-pharmacological interventions in 6,632 recognized rare diseases revealed only one such trial (see Kwakkenbos *et al.*, 2013).

Together, these sources emphasize the urgent need for the development, evaluation, and dissemination of behavioural and psychological interventions to support people with rare diseases. Here, we summarize the key challenges faced by intervention developers in rare diseases and, using xeroderma pigmentosum (XP) as a case example, propose solutions to these challenges by distinguishing between the novel aspects of rare diseases and those shared with more common problems.

Case study: Xeroderma pigmentosum

Xeroderma pigmentosum is a very rare autosomal recessive disorder in which affected individuals have a mutation in the genetic pathway responsible for the repair of DNA damage caused by exposure to ultraviolet radiation (UVR) in daylight (Fassihi *et al.*, 2016). XP has an incidence in Western Europe of approximately 2.3 per million live

births, although there are cross-country and cross-cultural differences in prevalence (Lehmann, McGibbon, & Stefanini, 2011). Symptoms can include extreme sunburn reactions following minimal sun exposure, abnormal pigmentation in sun-exposed areas, progressive neurological degeneration (sometimes necessitating full-time care), ophthalmological problems, and a 2,000-fold increase in the incidence of melanoma skin cancers (10,000-fold increase in non-melanoma skin cancers). There are eight complementation groups (XP-A to XP-G, and XP-V), which differ in their genetic and concomitant symptom profiles (Fassihi *et al.*, 2016). Diagnosis occurs in childhood for those with an abnormal sunburn reaction and later when the sunburn reaction is normal. The latter are often treated as non-XP melanoma patients until the frequency of skin cancer prompts further investigation and diagnosis. There is no cure for XP, and median life expectancy is 32 years (Bradford *et al.*, 2011). The most important part of clinical management involves rigorous photoprotection of the skin from UVR (Tamura, DiGiovanna, Khan, & Kraemer, 2014), which includes reducing time spent outside in daylight and achieving complete coverage using clothing and sunscreen when outside. UVR exposure and photoprotection are integral in determining prognosis (morbidity and mortality; Fassihi *et al.*, 2016).

Although no research into adherence to photoprotection in XP exists, observations of patients and their disease status/progression by the UK National XP clinical team during regular clinic visits suggest that protection is often inadequate. Consequently, a 5-year, mixed-methods study funded by the National Institute of Health Research (NIHR), under their rare diseases call, is underway to identify the predictors of poor photoprotection in patients with XP (phase I). This information will inform the development of a toolbox of evidence-based, individualized behavioural and psychological interventions to improve photoprotection and health outcomes (phase II). Initially, the intervention will be targeted at non-adherent adults with XP and will be tailored according to the information provided by each patient in phase I (see Walburn *et al.*, 2017 for phase I protocol). If effective, there may be potential for adapting the interventions for other XP groups (e.g., parents/carers); for use outside the United Kingdom, where factors such as the provision of clinic-based support, climate, and religion/culture are likely to differ; and for generalization to other rare diseases involving photosensitivity or that require rigorous, and often restrictive, self-management. The insights gained from such in-depth research into photoprotection behaviour may also be relevant to general population sun protection, where intervention effectiveness in improving protective behaviours and reducing UVR exposure has been limited (e.g., Rodrigues, Sniehotta, & Araujo-Soares, 2013; Williams, Grogan, Clark-Carter, & Buckley, 2013).

Challenges

The challenges associated with designing an intervention to improve photoprotection behaviour in patients with XP, or any rare disease, can be described under three broad categories:

1. *Rarity* – in the United Kingdom, there are ~100 patients who have been diagnosed with XP. Further, there is considerable heterogeneity in this small group, including varying ages and age of diagnosis, cognitive abilities (i.e., XP-related neurodegeneration, which limits the feasibility of research participation), and complementation groups (each of which involves heterogeneity in symptoms and severity). Photoprotection, and thus the need for, and type of, intervention, may also differ

according to these features, although this is assumed rather than known. Any attempt to quantitatively study this group is therefore going to be met with difficulties in achieving adequate statistical power to detect meaningful predictors of behaviour or between-group differences. Similarly, the conduct of a RCT to determine intervention effectiveness will be limited by the small population.

2. *Lack of availability of previous research* – typically, previous research would guide decision-making on methodological aspects of intervention design (e.g., definition and measurement of behaviour; selection of theoretical framework; likely causal mechanisms via which effects on behaviour/outcomes could be achieved). Scoping searches (Google Scholar, EBSCO, Web of Science, Medline) using various search terms in combination with XP returned few hits and no relevant empirical studies in adults (the target population) using any method. Thus, little is known about the experiences, impacts, or psychological characteristics of patients with XP (pre-requisites for intervention design), and no interventions exist to improve behaviour or outcomes in this population.

3. *Patient burden* – to conduct the necessary formative research to first understand and predict photoprotection behaviour, researchers are reliant on a small group of patients to participate in all methods, and with the hope that they remain in the study, as there is no opportunity to 'replace' participants if attrition occurs. In addition, study burden must be balanced with illness burden (e.g., frequent medical appointments, lifestyle restrictions). Having participated in phase I, the same group of participants will become the target population for the intervention, which means that piloting is not possible, as patients involved in the pilot either cannot participate in the trial or will do so 'contaminated'. Similarly, the use of certain data collection methods in an intensive phase I protocol (e.g., self-monitoring) may mean that intervention participants are no longer representative of a naïve group, which could affect implementation and dissemination outside of the trial. This is in stark contrast to research in many other behaviours and conditions, where the various phases are conducted in different samples drawn from the one larger target population.

Solutions for conducting formative research in rare diseases

'Best practice' intervention development typically involves following a systematic approach (a review is beyond the scope of this editorial; Araujo-Soares, Hankonen, Presseau, Rodrigues, & Sniehotta, unpublished data for a summary). Despite differences between approaches, the steps related to formative research – that is, questions about what needs to change (behaviour) and how such change might be achieved (mechanisms/theory) – are remarkably similar. Figure 1 summarizes these steps, focusing on the behaviour change wheel (Michie, Atkins, & West, 2014; which also encompasses the Theoretical Domains Framework), intervention mapping (Bartholo-mew Eldredge *et al.*, 2016), and the UK Medical Research Council guidance on the development and evaluation of complex interventions (Craig *et al.*, 2008). As empha-sized by each approach, the steps involved in intervention development are not necessarily linear. In Figure 1, we also outline specific adaptations that were needed to overcome the challenges in XP. Importantly, we are not advocating an entirely new approach for rare diseases – all the elements of best practice remain (e.g., public and patient involvement [PPI], stakeholder consultation) but the emphasis and reliance on different sources of information to provide answers to inform intervention development is necessarily different.

What is already known?

In the absence or shortage of previous research on the specific rare disease, it may be necessary to cast a wider and more creative search net to make meaningful use of the literature that is available on similar behaviours and conditions (see Figure 1 for examples). While similarities with other populations will inevitably exist, understanding the nuances of behaviour and predictors in the context of the target rare disease is integral to the successful matching of intervention targets, techniques, and content, and any tailoring. In XP, there are
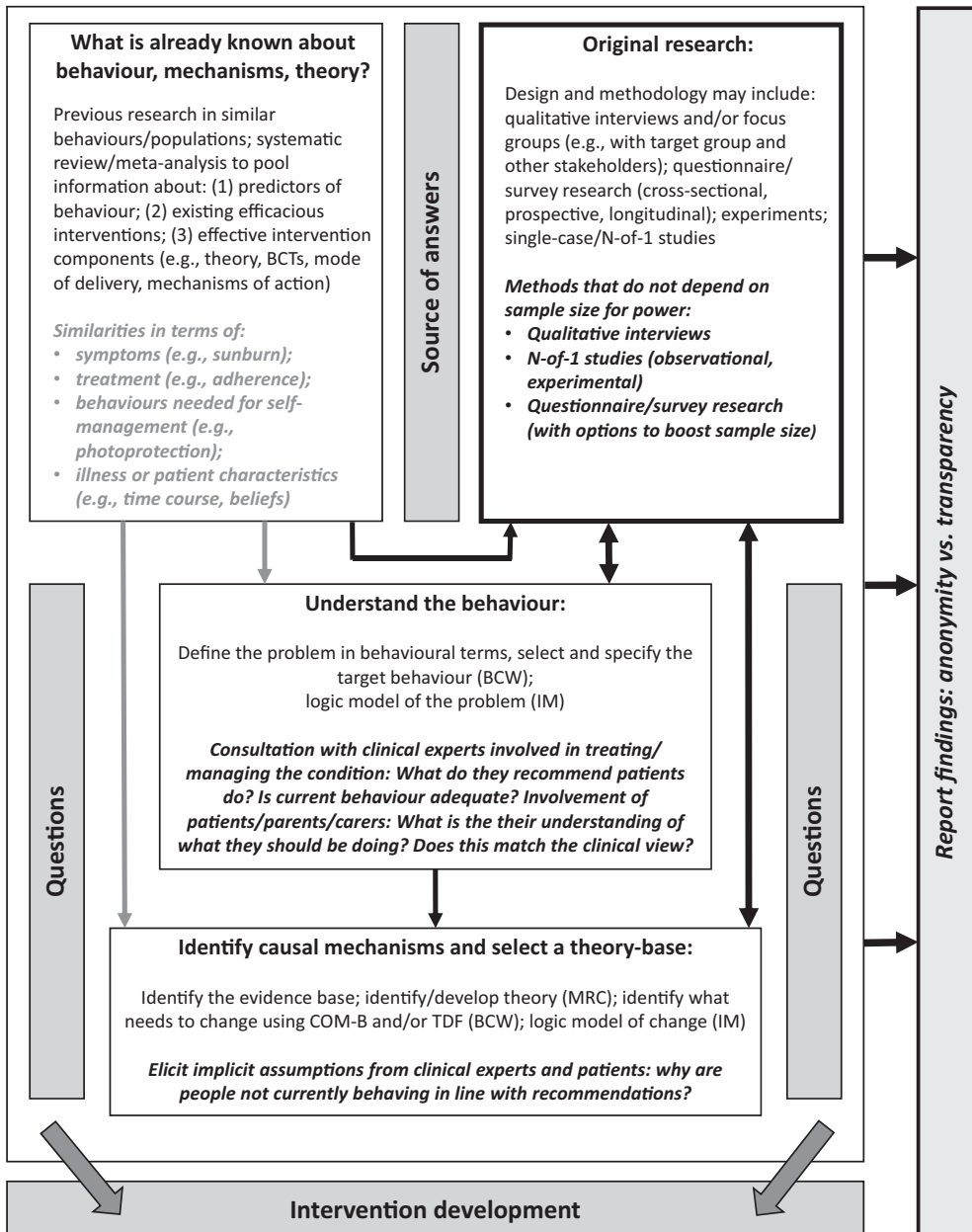

What is already known about behaviour, mechanisms, theory?

Previous research in similar behaviours/populations; systematic review/meta-analysis to pool information about: (1) predictors of behaviour; (2) existing efficacious interventions; (3) effective intervention components (e.g., theory, BCTs, mode of delivery, mechanisms of action)

Similarities in terms of:
- *symptoms (e.g., sunburn);*
- *treatment (e.g., adherence);*
- *behaviours needed for self-management (e.g., photoprotection);*
- *illness or patient characteristics (e.g., time course, beliefs)*

Source of answers

Original research:

Design and methodology may include: qualitative interviews and/or focus groups (e.g., with target group and other stakeholders); questionnaire/ survey research (cross-sectional, prospective, longitudinal); experiments; single-case/N-of-1 studies

Methods that do not depend on sample size for power:
- *Qualitative interviews*
- *N-of-1 studies (observational, experimental)*
- *Questionnaire/survey research (with options to boost sample size)*

Report findings: anonymity vs. transparency

Questions

Understand the behaviour:

Define the problem in behavioural terms, select and specify the target behaviour (BCW); logic model of the problem (IM)

Consultation with clinical experts involved in treating/ managing the condition: What do they recommend patients do? Is current behaviour adequate? Involvement of patients/parents/carers: What is the their understanding of what they should be doing? Does this match the clinical view?

Questions

Identify causal mechanisms and select a theory-base:

Identify the evidence base; identify/develop theory (MRC); identify what needs to change using COM-B and/or TDF (BCW); logic model of change (IM)

Elicit implicit assumptions from clinical experts and patients: why are people not currently behaving in line with recommendations?

Intervention development

Figure 1. Graphical summary of the steps involved in formative research for systematic intervention development and suggested adaptations and change in emphasis for rare diseases. *Notes:* Regular font (top of each box) = steps involved in existing approaches; bold/italic font (bottom of each box) = adaptations for rare diseases; lighter text and bolded boxes/arrows indicate additional changes in emphasis in rare diseases; BCTs = behaviour change techniques; BCW = behaviour change wheel; IM = intervention mapping; MRC = Medical Research Council guidance for the development and evaluation of complex interventions; COM-B = capability opportunity motivation-behaviour model; TDF = theoretical domains framework. Although understanding the target behaviour and identifying the causal mechanisms/selecting a theory base may happen in parallel (as both previous and original research contribute to answering these questions), a comprehensive understanding of the former will also enable the latter; depending on what is identified using previous and original research, the selection of a theory base may not involve using one theory to the exclusion of others – instead, the theory base may include constructs and mechanisms from various theories and in combinations that have not previously been tested (prior to your study), if this approach provides the best fit to the data gathered.

qualitative (additional/different behaviours) and quantitative (intensity) differences in what patients must do to achieve adequate photoprotection compared to other groups. For example, wearing a face visor or buff are forms of protection that will be foreign to the general population, and which likely carry additional barriers relating to comfort, visible difference, and stigma (Anderson, Walburn, & Morgan, 2017), and will differ according to contextual factors such as religion/culture. Regarding intensity, people with XP need to be fully protected from UVR during daylight, regardless of factors such as the weather (e.g., sun, cloud coverage), time of day (i.e., not only during higher risk times: 11 am-3 pm), and season (i.e., although cooler and with fewer daylight hours, protection is as essential in winter as summer), as well as when indoors if daylight is able to penetrate windows (e.g., car, office). In contrast, recommendations for the general population are focused primarily on sun protection in high risk contexts (i.e., summer/holiday periods, middle of the day). Given the cumulative nature of UVR-induced DNA damage in XP, short exposures also need to be accompanied by rigorous photoprotection, whereas a period of unprotected time in the sun is recommended for the general population to prevent vitamin D deficiency (Holick, 2007). Previous research can therefore provide a backdrop for decisions about the conduct of original research, but may not otherwise directly contribute to intervention development (denoted by grey text and arrows in Figure 1), where a more tailored approach matched to the specific context and behaviours will be required.

Original research
In rare diseases, original research is likely to be the major source of information contributing to understanding the behaviour and its casual mechanisms (denoted by bolded box in Figure 1). Methodologies that do not depend on sample size for power are particularly well suited for rare diseases. Qualitative interviews are a mainstay in many fields, and although not unique to rare diseases, represent a good starting point for gathering an in-depth understanding of the patient perspective (Green & Thorogood, 2014), from which other methodologies can build. Questionnaire research may be possible, if steps are taken to increase sample size (e.g., data collection in more than one site/organization/country; done in XP), as suggested in the context of improving quality of life for patients with the rare disease, scleroderma (Kwakkenbos *et al.*, 2013).

Finally, N-of-1 or single-case designs are recommended in rare diseases, as analysis is concerned with within-participant temporal and contextual variation and power is derived from repeated observations rather than the number of participants (McDonald *et al.*, 2017). The lack of generalizability (particularly when bespoke protocols are used) that is sometimes a criticism of N-of-1 is also less relevant in rare diseases, where personalized/tailored interventions are used and there is considerable overlap in the formative and intervention samples. In XP, data from an N-of-1 study were used to gain a comprehensive understanding of the target behaviour and to determine the intra-individual predictors of variation in behaviour over time. The former included describing the individual photoprotection behaviours and their relative degree of UVR protection; variability in protection, within-participants over time and within an outdoor occasion; and inferring the need for intervention based on the [in]adequacy of current levels of protection. Only with this detailed understanding could we define a clinically meaningful primary outcome, which allowed for the second task of identifying predictors of photoprotection (Sainsbury *et al.*, 2017).

In a mixed-methods project in a small population, balance needs to be struck between adequate coverage/specificity and patient burden. This contrasts with more common and well-researched conditions, where different constructs can be assessed in separate samples and previous research can aid the narrowing down of theoretical options. In XP, decisions about the match between methodology and construct were based on how much was known about the expression of the construct in patients and the ability of the team (research, clinical, PPI) to formulate a directionally unambiguous and succinct question. If the direction of the construct–behaviour relationship was known/assumed (e.g., habit), constructs were included in a quantitative methodology; if insufficient knowledge meant that the presence, nature, or direction of the relationship with photoprotection was unknown (e.g., stigma), these were probed in the interviews (Anderson *et al.*, 2017). Within the quantitative methodologies, the anticipated stability (cross-sectional survey with international data collection) or variation over time (N-of-1) of each construct informed decisions.

Understanding the behaviour and causal mechanisms

The involvement of stakeholders (e.g., patients, clinical experts) is even more crucial in rare diseases. Clinical recommendations regarding what patients *should* be doing (e.g., different forms of photoprotection in XP) may take a more prominent role in defining, operationalizing, and measuring the target behaviour within the original research (e.g., using purpose-designed measures). Experts can also help to identify potential causal mechanisms, by eliciting implicit assumptions about why certain patients adhere well, while others continue to place themselves at risk. While experts will not think about the problem or solution in 'logic model' terms, their wealth of patient-centred experience places them in a good position to generate informed hypotheses that can be tested and mapped to psychological theory. The XP clinical team held several causal beliefs – these included the severity of the sunburn reaction ('burners' would protect better than 'non-burners' due to the salience of consequences), age of diagnosis (adult diagnoses would be associated with worse photoprotection, as the adjustment to protection and lifestyle restrictions would be greater), and that risk perception was inaccurately based on how sunny it was. Collected data were then triangulated with that for which questions were generated by more standard means (i.e., previous research, common theoretical mechanisms) to contribute a more detailed knowledge of the behaviour and its drivers.

Reporting the findings

An additional consideration in rare diseases is balancing the need for transparent reporting that places the results in sufficient context, while preserving the anonymity of patients in small populations to guarantee them the same rights that members of a larger population would have when participating in research. This is particularly so given the focus on methodologies for which reporting tends to be at the individual rather than aggregate level (i.e., N-of-1 and interview quotes). Levels of anonymity might include ensuring that patients cannot be identified by their treating team, members of the public (e.g., friends/family/work colleagues), and that they cannot identify themselves or other patients. Here, we re-assigned participant ID numbers for publication; withheld demographic/clinical details if these could lead to identification (e.g., age, age of diagnosis, complementation group), as decided on a paper-by-paper basis and determined partly by the methodology (e.g., N-of-1 uses within-participant analysis so static characteristics are less informative for interpretation). Prior to submission, all papers will undergo a routine anonymity screen by the research nurse, who is familiar with all study patients.

Conclusion

Although the challenges of working with rare diseases can be exciting, they also pose several questions when considering recommendations for systematic intervention development. We have outlined some solutions to these challenges that we believe will help future researchers to conduct the necessary formative research to inform the development of behavioural and psychological interventions to support self-management and improve the health outcomes of individuals with rare diseases. Engaging in this process will ensure that interventions in rare diseases have the best chance of being effective; a concern that is perhaps even more important here, due to the impracticality and patient burden associated with repeating this process if it does not work.

Conflict of interest

All authors declare no conflict of interest.

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