Title

Developing and evaluating rare disease educational materials co-created by expert clinicians and patients: the paradigm of congenital hypogonadotrophic hypogonadism

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ABSTRACT

Background: Patients with rare diseases face health disparities and are often challenged to find accurate information about their condition. We aimed to use the best available evidence and community partnerships to co-create patient education materials for congenital hypogonadotrophic hypogonadism (Kallmann syndrome) and evaluate end-user acceptability. Expert clinicians, researchers and patients co-created the materials in a multi-step process. Six validated algorithms were used to assess reading level of the final product. Comprehensibility and actionability were measured using the Patient Education Materials Assessment Tool via web-based data collection. Descriptive statistics were employed to summarize data and thematic analysis for analyzing open-ended responses. Subsequently, translation and cultural adaption were conducted by clinicians and patients who are native speakers.

Results: Co-created patient education materials reached the target 6th grade reading level according to 2/6 (33%) algorithms (range: grade 5.9-9.7). The online survey received 164 hits in 2 months and 63/159 (40%) of eligible patients completed the evaluation. Patients ranged in age from 18-66 yrs (median 36, mean 39±11) and 52/63 (83%), had adequate health literacy. Patients scored understandability at 94.2% and actionability at 90.5%. The patient education materials were culturally adapted and translated into 20 languages (available in the supplemental materials).

Conclusions: Partnering with patients enabled us to create high-quality patient education materials that met patient- identified needs as evidenced by high end-user acceptability, understandability and actionability. The web-based evaluation was effective for reaching dispersed rare disease patients. Combining dissemination via traditional healthcare professional platforms as well as patient-centric sites can facilitate broad uptake of culturally adapted translations. This process may serve as a roadmap for creating patient education materials for other rare diseases.

BACKGROUND

The landmark 2009 report from the European Organization for Rare Diseases (EURORDIS) brought to light the many challenges faced by patients with rare diseases [1]. Delays in diagnosis, difficulty finding information about their condition and inadequate access to expert care are frequent patient experiences. Indeed, some have posited that living with a rare disease places one in the realm of health disparities [2]. Physical and psychological morbidity can be significant and feelings of isolation and powerlessness can further undermine quality of life [3]. Importantly, potential means to overcome these challenges include using the internet to connect dispersed patients with expert care and community engagement to help empower patients who feel marginalized by the healthcare system [4-6].

One such rare disorder is congenital hypogonadotrophic hypogonadism (CHH, ORPHA174590). Based on a study of French conscripts, CHH occurs in approximately one in 4,000-10,000 [7]. It is clinically characterized by incomplete (or absent) puberty and infertility resulting from insufficient secretion or action of gonadotrophin releasing hormone (GnRH) - the master hormone of the reproductive axis [8]. Genetic defects that disrupt migration of GnRH neurons may additionally manifest as absent or defective sense of smell (anosmia or hyposmia) - termed Kallmann syndrome/olfacto-genital syndrome (ORPHA478). Genetic and phenotypic overlap exists between these two entities, yet patients with Kallmann syndrome are more likely to exhibit additional non-reproductive associated phenotypes (i.e. skeletal defects, renal agenesis, cleft lip/palate, deafness) compared to their normosmic counterparts.In the context of an international network of leading clinicians/geneticists/researchers focused on CHH [9], we have previously developed patient partnerships and conducted a needs assessment that leveraged engagement with patient support groups, social media and online data collection [10]. In parallel, we developed a web-based platform [9] with resources for patients to find expert clinicians and peer-to-peer support. Additionally, consensus guidelines for the diagnosis and treatment of CHH were created using an evidence-based approach [8].

Engagement and co-creation have been effectively used in diverse fields including business, design and computer science (i.e. user-centered design) as a means to spur innovation, adoption and foster sustainability [11, 12]. Therefore, the aim of the present study was to partner clinical experts and patients to co-create high-quality patient education materials (PEM) that respond to the issues and questions most important and relevant to patients. Secondary aims included evaluating the readability of the PEM and end-user acceptability (i.e. understandability and actionability) as well as to disseminate these materials widely across different countries and cultures.

METHODS

PEM development

A community based participatory research framework was selected to guide the development of the patient education material (PEM) for its relevance to patient empowerment and health disparities [13]. The Patient advocacy Working group of the European network focused on CHH (COST Action BM1105, "GnRH Deficiency: Elucidation of the neuroendocrine control of human reproduction") [9] worked closely with online patient community leaders (i.e. moderators of online patient support sites) to identify key PEM content areas and topics based on the most frequently asked questions on social media sites (supplemental materials) as well as from a previously conducted patient needs assessment [10]. Clinical information was drawn from the evidence-based consensus statement on the approach to diagnosis and treatment of CHH [8]. The PEM development was an iterative process (**Figure 1)** involving multiple stakeholders including patients, patient support groups, clinicians and researchers spanning the fields of endocrinology, andrology, nursing and genetics. At each step, input and feedback were used to refine and modify the PEM.

Readability assessment

To assess reading level of the produced PEM, we subjected the final version to several validated measures evaluating readability: Flesch Reading Ease Formula (evaluates sentence length and number of syllables per word), Flesch Kincaid Grade Level (converts the Flesch reading ease formula to a grade level), Gunning Fox Index (calculates a weighted average of the number of words per sentence and long words to determine grade level), Coleman Liau Index (uses number of characters rather than syllables to determine grade level), Simple Measure of Gobbledygook (SMOG, a modification of the Gunning-Fog Index it calculates grade level based on the number of words with 3 or more syllables) and the Automated Readability Index (ratio of diffifult words and sentences to provide an estimated age range and grade level) [14].

End-user acceptability

To evaluate end-user perspectives of adults with CHH (18 years and older), we used an online data collection (SurveyGizmo™) and recruited a convenience sample of patients via postings on closed/private CHH social media group (Facebook™), as well as notifications in patient support group meetings and RareConnect [15]. This social media approach has been previously shown to be an effective means of recruitment for this rare disease patient population [10]. The survey included questions on patient demographics, past healthcare interactions and a brief assessment of healthcare literacy that has been validated against longer gold-standards metrics [16, 17].

After reviewing a pdf of the PEM, participants were asked to complete the Patient Education Materials Assessment Tool (PEMAT). This instrument was developed and validated by the U.S. Department of Health & Human Services Agency for Health Research & Quality to evaluate print and audiovisual educational materials [18]. The unique aspect of the PEMAT is that it incorporates other additional elements that are not assessed in traditional readability formulas. Patients select agree, disagree or not-applicable for 17 items relating to understandability (the ability to process key messages) and 7 items on actionabilty (the

ability to identify what one can do to manage their condition). Items rated as agree are given a score of 1, disagree 0 and cumulative scores are expressed as a percentage (total score/possible total X 100). Initial psychometric evaluation of the PEMAT has demonstrated strong internal consistency, good reliability, and initial evidence of construct validity [19]. Survey respondents were also given an opportunity to provide free text comments (i.e. critiques and suggestions) after completing the PEMAT questions.

Statistical analyses

The survey was alpha tested by patients in two rounds to identify and correct any bugs prior to online launch. Descriptive statistics were used to report summary findings. To assess for potential response bias, Student's t test and Chi square test were used to compare demographic characteristics of patients who completed the evaluation with those who did not (partial completion). Thematic analysis [20] was employed to codify and analyze open-text responses NVivo11 (QSR International PSY Ltd., Melbourne Australia). The study was reviewed and approved by the ethics committee of the University of Lausanne and participants provided opt-in online consent.

Dissemination

The final step of this process was to disseminate the PEM to reach the broadest possible audience. This included using native speakers (i.e. expert clinicians, medical translators) from across the European network to provide versions in multiple languages. Particular attention was given to finding appropriate terms and examples for the translated PEM to make them culturally sensitive and not simply verbatim translations. The final materials will be distributed via traditional means to reach healthcare professionals (i.e. peer-review publication, professional meetings, individual providers' websites, and via the COST Action website [9]). In parallel PEMs will be distributed via patient support groups including online social media (Facebook™, Twitter™, patient blogs) and publicized on internet platforms targeting the rare disease community including the EURORDIS initiative RareConnect [15].

RESULTS

PEM development

Patient partnerships were used to identify key topics and to target issues most important to patients as well as to contribute content. A working group of the network (Patient Advocacy Working Group) created a topic list based on the consensus statement guidelines [8]. Additional items were drawn from focus group discussions with patients held in the context of patient support meetings (organized with patient leaders) as part of the prior needs assessment [10] (**Figure 1A**). Patient collaborators also contributed lists of "frequently asked questions" as well as topics that were recurrent in social media threads and chat room discussions. Common questions include: what causes CHH?, why didn't I go through puberty? Why can't I smell? Is it curable? Can I have children? Will my children have CHH? (see supplemental materials). The drafted material version 1.0 (V1.0) went through two subsequent revisions to refine language, wording and selection of images via email and the PEM was finalized in a face-to-face meeting prior to vetting with the broader network (**Figure 1D**). During this development process it was sometimes challenging to balance the input and feedback from clinicians and patients to find the right balance and depth of information provided. Indeed, the face-to-face meeting was valuable for arriving at consensus as opinions were conflicting at times during the process and this was not easy to reconcile via email.

Readability levels

Readability was evaluated using 6 different validated algorithms that are widely used to assess reading level (**Table 1**). These employ different formulas that use word length and complexity (i.e. the number of characters or syllables in words, sentence length) to calculate an average grade level needed to understand the material. Most patients read at an 8-9th grade reading level [21]. However, expert recommendation has identified the target reading level at 6th grade (i.e. an 11 year-old child) [22]. Two of the six algorithms scored the PEM at

the target grade level (Flesch Kincaid Grade Level: 5.9, Automated Readability Index: 6.1). The mean grade level across instruments was 8.0 (**Table 1**), indicating that more work could be done to enhance readability. However, one challenge in doing this is the number of complex words (i.e. hypogonadism, cryptorchidism, infertility, etc) that were deemed important by clinicians and patients alike to include and define in lay terms.

Participants

Following patient alpha testing to identify and correct bugs in the online evaluation, the survey was launched and remained open for 8-weeks. During this period, 164 hits were registered. In total, 38 (23%) were "one-click" entries who passed the opt-in consent but did not enter demographic information. Responses of five participants were excluded (age <18yrs). More than a third of respondents (58/164, 35%) partially completed the evaluation (i.e. demographics up to viewing the PEM) and 63 (38%) completed the entire PEM evaluation (**Figure 1E**). Characteristics of survey respondents are depicted in **Table 2**. Notably, the predominance of male responders (2:1) is keeping with the striking sexual discordance in CHH [8]. Overall, patients were well-educated (46/63, 73% achieving university or higher) and by-and-large exhibited adequate health literacy (52/63, 82%). Notably, the mean age of diagnosis was 20.9±6.4 years (range: 10-40, median 19) suggesting that many patients are diagnosed quite late. In terms of prior healthcare interactions, more than half (39/63, 62%) had either a consultation or had received care at a specialized academic center. In total, 36/63 (56%) had undergone genetic testing yet only 12/63 (19%) reported having had genetic counseling. We found no significant differences between those who completed the evaluation and the partial completers in terms of age (p=0.30), sex (p=0.37), education (p=0.94), health literacy (p=0.15), or being seen at an academic center (p=0.09).

End-user acceptability

Patients gave the co-created PEM high scores on understandability (range: 88.9-97.5%, total mean: 94.2%) which includes content, word choice/style, use of numbers, organization, layout/design and visual aids (**Table 3**). The lowest rating (88.9%) was linked with being uncluttered which was commented on in the free text field by three patients (i.e. having more white space). Similarly, patients gave high scores on actionability (overall mean: 90.5%). The lowest score was assigned to explaining how to use charts, graphs, or diagrams to take action and manage the condition. Together the high scores on both understandability and actionability indicate high end-user acceptability.

Overall we received comments from 45/63 (71.4%) patients. Comments were coded according to themes and sorted into categories. In total, 52 concepts were identified from the 45 comments clustering into five categories (**Table 4**). The most frequent sentiments were expressions of thanks/approval (n=19, 37%) followed by content (i.e. treatment, infertility, and psychological aspects) n=11 (21%), format (i.e. use of simple language, spacing) n=10 (19%), personal concerns (n=9, 17%) and three comments underscored the importance of translating the PEM to make it available to more patients.

Broad dissemination

Native speakers from across the European network made culturally adapted translations. In some instances local patients contributed to this translation and adaption process. The translated PEMs required cultural adaption in some instances to help make them more relevant for the target audience. For instance, a small cherry was used to describe the size of the pituitary gland in the Hungarian version, the Chinese version was altered as “what you should know” was not culturally appropriate, and terms describing depression were adapted in the Polish version to enhance comprehension by the lay public. Every effort was made to keep the entire content of the PEM in the translated versions. When text length expanded the images were adjusted accordingly to maintain a 5-page document. PEM are now available in 20 languages: English, Bulgarian, Chinese, Danish, Dutch, French, German,

Greek, Hebrew, Hungarian, Italian, Korean, Polish, Portuguese, Romanian, Russian, Serbian, Slovenian, Spanish, and Turkish (**Supplemental Materials**). Dissemination plans will target healthcare professionals and patient-centric avenues such as social media and patient support sites.

DISCUSSION

The aim of this study was to engage patients and co-create PEM that respond to what matters most to patients. Subsequently, we evaluated the readability and end-user acceptability of the PEM and sought to widely disseminate the translated PEM across different countries and cultures. Patients living with a rare disease face health disparities [2] and patient engagement has been identified as potential means to empower this patient population [4-6]. Interestingly, patient engagement has recently been gaining attention in the context of orphan drug development [23]. However, the extent of patient engagement varies widely. A 2014 systematic review of patient engagement for research on rare diseases found engagement is typically unidirectional - involving patients in consultative roles and rarely in creative aspects or in terms of dissemination [24]. The present study is unique in that we used a participatory process to co-create PEM with patients; we then evaluated the PEM produced by this collaboration, and worked with patient groups to facilitate dissemination to the largest possible audience.

We previously partnered with online patient community leaders to identify the unmet health and informational needs of patients with congenital hypogonadotrophic hypogonadism (CHH) and Kallmann syndrome [10]. In the present study, the partnership was more clearly bi-directional as patients were not simply providers of opinions; rather they contributed directly in co-creating the PEM in an iterative process. Notably, patient knowledge and expertise emerges from the day-to-day experiences of living and coping with a rare condition and therefore is inherently different from the expertise of healthcare professionals [25]. Recently, a study examining online exchanges among patients with rare adrenal disorders found that

information and support were central elements in peer-to-peer exchanges [26]. Moreover, the authors noted that patient-centered care could be enhanced by better integrating patient knowledge with the care provided by professionals. In the present study, developing the PEM was a true partnership that recognized patient expertise as unique and complementary to expert clinician knowledge. We believe that this co-creation contributed to the high acceptability ratings by patients.

This evaluation process of the co-created PEM has limitations. The evaluation was only conducted on the English version. As such, the findings are not completely transferable to the other translated versions despite the inclusion of patients in developing some of the translations. Moreover, the additional validation step of back translating the other versions was not conducted and this could be viewed as a limitation. We only assessed readability once the materials had been finalized, not during the development process. In future studies, this testing could be incorporated earlier in the development process to improve the reading level of developed PEM. While the evaluation was overwhelmingly positive and a fairly sizeable sample was reached (for a rare disease population), the patients completing the evaluation were quite well-educated and exhibited high levels of health literacy. Accordingly, our ability to draw inferences to a broader population of lower literacy patients is limited. This may reflect a bias of using a web-based survey - as perhaps those using the web may have higher literacy levels. However, recruiting sufficient numbers of patients for rare disease studies has been a long-standing challenge [27, 28]. Therefore, we used a web-based approach to overcome this barrier but note that such an approach entails a potential risk of bias.

The Pew Foundation's published report on health and the internet indicates that patients living with a rare disease are internet power users who are most likely to seek information about their condition online and find support from other patients using social media [29]. Based on our previous success combining patient partnerships and social media for the

441 online needs assessment [10], we employed a similar approach in the present study to
442 reach a relatively large sample (n=63) over 8-weeks. These experiences suggest that web-
443 based platforms are an effective means to reach and connect rare disease patients. Thus,
444 the opportunities afforded by the internet and social media may provide novel avenues for
445 crowdsourcing solutions as well as offering a shared venue for either clinician- or patient-led
446 collaborations to improve quality and add value to the healthcare system [5, 30]. The
447 European Union Committee of Experts on Rare Diseases (EUCERD) recommendations for
448 Centers of Expertise underscore the importance of collaboration with patient organizations to
449 provide information that is at once accessible and adapted to patient needs [31]. For many
450 rare diseases, such as CHH/Kallmann syndrome, formal organized patient support
451 organizations do not exist. As such, web-based approaches and social media provide a
452 critical means to broadly reach patients, identify priorities and incorporate their perspectives
453 and knowledge into care. This may be particularly advantageous in light of the movement to
454 form European Reference Networks for rare diseases [32, 33].
455
456 The final step in this co-creation process was to engage in bi-directional dissemination. This
457 has been identified as a shortcoming in much of the patient engagement research conducted
458 in the context of rare diseases [24]. Through the work of members of the Network and
459 patients alike, materials were adapted and translated into 20 languages by native speakers.
460 This collaborative process is essential for ensuring that information provided to patients is
461 culturally adapted and sensitive – a key element for Centers of Expertise [31]. In parallel to
462 traditional healthcare professional outlets (e.g. scientific meetings, peer-review publication)
463 patient participants are distributing materials directly to other patients via social media and
464 postings on centralized patients sites [15]. The co-created PEM (in multiple languages) is a
465 critical component of the list of patient resources available on the website of the European
466 network comprising a virtual empowerment toolkit for patients and families [9]. Available
467 information includes listings of international specialized referral centers, genetic testing labs,
468 clinical trials, and peer-to-peer support as well as a portal for a patient registry. We are

utilizing both professional-oriented avenues and more patient-oriented social media outlets to hopefully reach unprecedented numbers of patients and clinicians and overcome traditional roadblocks of implementation into practice [34-36].

CONCLUSIONS

Partnering with patients enabled co-creation of high-quality PEM while social media and web-based data collection facilitated timely evaluation by a dispersed patient population. We believe that partnering with expert patients was an empowering experience and provides valuable contributions for developing patient-centered approaches to care. We envision this work will serve as a roadmap for those wishing to engage in a co-creation process and will help inform projects aimed at improving care for patients living with a rare disease.

LIST OF ABBREVIATIONS

CHH: congenital hypogonadotrophic hypogonadism

EUCERD: European Union Committee of Experts on Rare Diseases

EURORDIS: European Organization for Rare Diseases

COST: European Cooperation in Science and Technology

PEM: patient education materials

PEMAT: Patient Education Materials Assessment Tool

SMOG: Simple Measure of Gobbledygook

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study (protocol #233/13) was reviewed and approved by the Commission Cantonale d'ethique de la recherche sur l'être humain which is the institutional review board (Ethics Committee) associated with the University of Lausanne. All survey participants provided opt-in electronic consent prior to completing the online evaluation.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIAL

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

COMPETING INTERESTS

The authors have no financial or non-financial competing interests to declare.

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AUTHOR'S CONTRIBUTIONS

AD conceived the study and participated in study design, conduct, analyses and drafted the manuscript. RQ, NP and NS helped draft the educational materials with patients. All authors helped revise the materials and contributed to developing culturally relevant translations. All authors read and approved the final manuscript.

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FIGURE LEGEND

Figure 1. Study Schema. PEM were co-created in a multi-step process. (A) Three main sources were used for PEM development. (B) Members of the Patient Advocacy Working Group and patient collaborators identified topics for the PEM in an iterative process. (C) The initial draft was created and revised based on patient input. (D) PEM (V2.0) was circulated to the Clinical Working Group and Genetics Working Group members for comment and revised accordingly with patient validation in two rounds. (E) PEM (V4.0) were evaluated by patients recruited via social media (private/closed Facebook groups), patient support meetings and via RareConnect [12]. (F) Following evaluation materials were culturally adapted and translated to 20 languages and distributed in avenues targeting healthcare professionals and patients. PEM: patient education materials, V: version.