Communications in rare diseases – the current landscape and future directions of communications about the post-commercial launch of orphan drugs.

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Abstract

Rare diseases are often chronic and progressive conditions that can be life limiting. The majority of these diseases are genetic in origin and affect a small number of people. In the EU a disease is described as rare when it affects less than 1 in 2,000 people. In the UK there are around 3.5 million people affected by a rare disease. Rare diseases present unique challenges including delays in diagnosis, lack of expertise and investment in research and education about the disease. The unique nature of rare diseases means communications require innovative approaches to ensure the needs of the rare disease patient are met. This is true in terms of the post–commercial launch of orphan drugs to treat rare diseases. Communications about these treatments must be delivered in an effective way, ensuring the drug can be provided to meet the needs of the patient. Communications require input from all stakeholders, including patient groups, pharmaceutical and healthcare communication companies. Open Health, a healthcare communications company with expertise in rare diseases, will be used as a case study to conduct a critical review. This will assess the current landscape and future directions of communications of rare diseases in relation to the post-commercialisation of orphan drugs. This will involve thematic analysis of articles and interviews conducted at Open Health. Conducting this critical review will inform current practice, helping to improve the communications of complex scientific information about rare diseases and orphan drugs for the benefit of the patient.

Introduction

Rare diseases are conditions that affect a small number of people (Richter et al., 2015; Rinaldi, 2005; Schieppati et al., 2008). These conditions are normally chronic and or progressive in nature and limit the lives of those affected, associated with significant burdens that are physical, emotional and economic (Melnikova, 2012; Price, 2016; Schieppati et al., 2008; Urwin et al., 2016). These burdens not only impact the individual but society as a whole (Price, 2016; Schieppati et al., 2008).

It is believed there are between 5,000 to 8,000 rare diseases, generally defined according to prevalence thresholds (Richter et al., 2015; Schieppati et al., 2008). These rare diseases are diverse and can affect any bodily system (Hansen, 2012; Schieppati et al., 2008). In the EU rare diseases are defined as conditions affecting less than 5 in 10,000 people (European Commission, 2014; Lampert et al., 2016; Price, 2016). This equates to 1 in 17 having a rare disease in the EU, or between 27 to 36 million people (European Commission, 2014; European Medical Agency, 2019a; Rare Disease UK, 2018). In the UK it is believed rare diseases affect around 3.5 million people (Rare Disease UK, 2018). In the US, rare diseases are defined as conditions affecting less than 200,000 people, affecting up to 30 million people (Evaluate, 2019; Genetic and Rare Diseases Information Center, 2017; Lampert et al., 2016). Although rare diseases are individually rare based on prevalence thresholds, collectively

they impact a significant number of people, with some rare diseases having a higher prevalence than others, effecting up to 400 million people globally (Boice et al., 2013; Melnikova, 2012; Pogue et al., 2018; Richter et al., 2015; Schieppati et al., 2008; Valdez et al., 2016).

The majority of these rare diseases have a genetic origin and can be divided into rare cancers and other rare diseases (Hansen, 2012; Melnikova, 2012; Urwin et al., 2016). These rare diseases can have obvious phenotypic traits, whilst others are less obvious (Hansen, 2012; McClellan and King, 2010). For most rare diseases, symptoms appear in childhood, with some appearing in adulthood (Hansen, 2012; Rinaldi, 2005). Around 20% of cancers are rare and affect less than 6 in 100,000 people, including familial melanoma, multiple melanoma and thyroid cancer, with all childhood cancers being rare (Kotecha et al., 2015; Pillai and Jayasree, 2017).

Other more common rare diseases include cystic fibrosis, Duchenne Muscular dystrophy (DMD), α1 antitrypsin deficiency, Hemophilia, Beta-Thalassemia, Adenosine deaminase deficiency (ADA) and inherited retinal dystrophy (Alliance for Regenerative Medicine, 2019; Melnikova, 2012; Schieppati et al., 2008).

Due to the nature of rare diseases, they present unique challenges that can lead to inadequate management, treatment and support (Limb et al.,

2010; Liuccio et al., 2015; Urwin et al., 2016). Common challenges for rare disease patients include lack of knowledge and expertise about the disease, delays in diagnosis, limited treatment options, lack of access to specialist treatment centres and inadequate care and management pathways (AMICULUM, 2014; Benjamin et al., 2017; Evans, 2018; Giannuzzi et al., 2017; Liuccio et al., 2015). These challenges affect families and carers too, with significant financial, psychological and social impacts on their lives (Anderson et al., 2013; Boice et al., 2013; Price, 2016; Schieppati et al., 2008; Simpson, 2016).

Rare diseases are often referred to as orphan diseases as they were ignored by the general public, research community, medical community and pharmaceutical industry for many years (Pogue et al., 2018; Price, 2016; Schieppati et al., 2008). There are many reasons why the study of rare diseases has been a challenge, including small patient populations, heterogeneity of disease, incomplete understanding of the disease and their often progressive nature (Benjamin et al., 2017; Lampert et al., 2016; Pearson et al., 2018; Price, 2016; Raffai and Timmis, 2017).

The term orphan drug is therefore used to describe any drug that is developed or used to treat a rare disease (Benjamin et al., 2017; European Medical Agency, 2015; Pogue et al., 2018). In order for a drug to be defined as and be granted orphan drug status there are a number of criteria that must be met (Joppi et al., 2016; Lampert et al., 2016; Price,

2016; Wellman-Labadie and Zhou, 2010). In the EU this can be granted if the drug is for the diagnosis, prevention or treatment of a condition affecting less than 5 in 10,000, where marketing is not likely to generate good return without incentives (European Medical Agency, 2015; Joppi et al., 2016; Lampert et al., 2016). The U.S Food and Drugs Administration (FDA) has similar criteria for orphan drug status with the major difference being that the condition affects less than 200,000 people (Lampert et al., 2016; Wellman-Labadie and Zhou, 2010).

Development of orphan drugs was seen as, and is still largely unattractive as development is associated with high costs, limited returns and high failure rates (Melnikova, 2012; Pogue et al., 2018; Price, 2016). Whilst this is still largely true, the introduction of legislation, regulation and acts across different countries and jurisdictions has provided incentives to develop orphan drugs (Darrow et al., 2018; Lampert et al., 2016; Melnikova, 2012; Pogue et al., 2018; Price, 2016). The introduction of the orphan drug act in the US in 1983 aimed to provide financial incentives for the development of orphan drugs through tax credits, fee reductions, grant programs and seven years marketing exclusivity once an orphan drug has been approved (Darrow et al., 2018; Giannuzzi et al., 2017; Lampert et al., 2016; Melnikova, 2012; Price, 2016). Marketing exclusivity means that regulatory bodies, for example the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK cannot approve the same orphan drug for the same disease in the prescribed period (European

Medical Agency, 2015; Giannuzzi et al., 2017; Price, 2016). In the EU, the EC regulation EC 141/2000 was introduced in 2000 (European Medical Agency, 2015; Lampert et al., 2016; Price, 2016). This provided incentives for orphan drug development in a similar way to the orphan drug act through fee reduction, procedural and protocol assistance at a reduced fee, funding for research and ten years marketing exclusivity (European Medical Agency, 2015; Giannuzzi et al., 2017; Lampert et al., 2016; Price, 2016).

Orphan diseases are increasingly seen as providing unique, novel and niche opportunities for pharmaceutical companies to develop drugs for a population with a large unmet need (Giannuzzi et al., 2017; Julkowska et al., 2017; Liuccio et al., 2015; Schieppati et al., 2008).

Through the introduction of these initiatives the climate for orphan drug development has changed massively, with many drugs reaching marketing authorisation or the end stage in the development process (Alliance for Regenerative Medicine, 2019; Evaluate, 2019; Giannuzzi et al., 2017; Lampert et al., 2016; Price, 2016; Richter et al., 2015). The marketing authorisation or post-commercial launch of an orphan drug describes the stage when a drug has been approved for market and can be prescribed to patients (Darrow et al., 2018; European Medical Agency, 2019b; Giannuzzi et al., 2017; Lampert et al., 2016; Melnikova, 2012). Once an orphan product has been authorised, post-marketing

authorisation or post-approval studies occur to assess it's safety and efficacy (European Medical Agency, 2019c; Lampert et al., 2016; Price, 2016; U.S Food and Drugs Administration, 2018). Without such studies a drug may be removed from market with patients no longer able to access the medicine (Darrow et al., 2018; Lampert et al., 2016; U.S Food and Drugs Administration, 2018).

As of 2019 14 gene therapies, cell therapies and tissue engineering products have been granted marketing authorisation in Europe for the treatment of a number of orphan diseases, with the amount of approvals set to increase in the next few years (Alliance for Regenerative Medicine, 2019; Benjamin et al., 2017; Evaluate, 2019). These include Kymriah for B-cell acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL), LUXTURNA for inherited retinal dystrophy and Zynteglo for Beta thalassemia (Alliance for Regenerative Medicine, 2019; Evaluate, 2019).

The growth in research and development of orphan drugs for both rare oncology and non-oncology diseases is predicted to increase over the next few years (Benjamin et al., 2017; Evaluate, 2019; Melnikova, 2012). It is predicted that orphan drugs will account for one fifth of prescription drug sales by 2024, with growth predicted at around 12.3% between 2019 to 2024, reaching $242 billion in sales (Evaluate, 2019). The top products for worldwide orphan drug sales in 2024 are predicted to include Imbruvica

for oncology, Hemlibra for Haemophilia A and Darzalex for multiple mylenoma (Evaluate, 2019).

The growth in orphan drugs will make effective communications vital to ensure the success of these drugs (Alliance for Regenerative Medicine, 2019; Benjamin et al., 2017; Darrow et al., 2018; Evaluate, 2019; Lampert et al., 2016; Schieppati et al., 2008).

Important factors in the communications around rare diseases and orphan drugs

Factors that have been suggested to play a role in the success of communications about an orphan drug once it comes to market include, high quality information and pharmacovigilance, use and integration of patient registries, quality, accuracy and comprehensiveness of evidence available and a clear dialogue and collaboration between all stakeholders on a national and international level (Ambrosini et al., 2018; Bellgard et al., 2017; Benjamin et al., 2017; Jiménez et al., 2018; Lochmüller et al., 2017; Milne and Ni, 2017; Morel and Cano, 2017; Mulberg et al., 2019; Price, 2016; Torrent-Farnell et al., 2018; Woodward et al., 2016). One of the most important factors in the communications and success of an orphan drug is taking a patient-centric approach to communications (Charles, 2014; Julkowska et al., 2017; Mulberg et al., 2019; Raffai and Timmis, 2017). This should occur across the whole patient pathway for

rare diseases, with communications meeting the individual needs of the patient and engaging with patient advocacy groups and other relevant stakeholders (AMICULUM, 2014; Blay et al., 2016; Charles, 2014; Levinson, 2019; Lochmüller et al., 2017; Lynn et al., 2017; Morel and Cano, 2017; Raffai and Timmis, 2017, 2017).

High-quality patient-centric real world data has been found to be important for effective communications and should take advantage of innovative analytical and modelling techniques (Benjamin et al., 2017; Morel and Cano, 2017; Mulberg et al., 2019; Torrent-Farnell et al., 2018).

Creative communication solutions utilising multiple channels taking advantage of infographics, social media and virtual communities have been suggested to be important for successful communications (Jiménez et al., 2018; Julkowska et al., 2017; Lynn et al., 2017; Milne and Ni, 2017; Morel and Cano, 2017). Narratives have also been found to be important, providing a clear context and allowing for an open conversation and engagement with all stakeholders (Lynn et al., 2017; Morel and Cano, 2017).

Challenges to communications

Rare diseases present unique challenges that can effect the success of rare disease and orphan drug communications, including a lack of disease awareness and knowledge from health care providers (HCPs), inadequate diagnosis, small patient populations and limited clinical data at the time of drug approval (AMICULUM, 2014; Blay et al., 2016; Budych et al., 2012; Hansen, 2012; Price, 2016). For rare diseases, centralised knowledge is often lacking, with patients becoming experts in their own disease (Morel and Cano, 2017; Polich, 2012; Raffai and Timmis, 2017).

A lack of understanding about the patient pathway and journey presents challenges and can lead to limited patient-centric communications, not taking into account the patient perspective (Goetghebeur et al., 2017; Levinson, 2019; Raffai and Timmis, 2017; Urwin et al., 2016). This often leads to communications lacking personalised and user-friendly content across the rare disease patient pathway, present in rare disease management, treatment and health technology assessment (HTA) processes (AMICULUM, 2014; Goetghebeur et al., 2017; Raffai and Timmis, 2017; Urwin et al., 2016). By not making the patient central to communications, this limits the reach and engagement with all stakeholders (AMICULUM, 2014; King and Hoppe, 2013; Levinson, 2019).

Other communication challenges and issues that have been found include over promotional communication campaigns and a lack of multi-channel communication strategies (AMICULUM, 2014; Morel and Cano, 2017). However, in terms of multi-channel strategies, these can be overcomplicated, with too much information and a lack of strategic alignment (AMICULUM, 2014; Levinson, 2019). A lack of consistent information and adaption of communications for a global network can limit the effectiveness of communications (AMICULUM, 2014; Levinson, 2019).

In relation to communicating data, using the EVIDEM reflective criteria framework to assess HTA processes, it was found that data and orphan drug value decisions are often presented in a bland and functional way, lacking visual expression that could be more easily understood by a variety of stakeholders (Goetghebeur et al., 2017). Having a clear narrative around value decisions for orphan drugs has been suggested as a way to allow for more effective communications, adding a more natural approach to HTA value decisions (Goetghebeur et al., 2017).

Differences in review processes for drugs and regulatory definitions between healthcare systems within and between different countries can present challenges to communications (Darrow et al., 2018; Lampert et al., 2016; Torrent-Farnell et al., 2018). This is because the individual needs and processes in different countries and jurisdictions around communications may not be taken into account (Darrow et al., 2018;

Lampert et al., 2016; Torrent-Farnell et al., 2018). In addition, a lack of standardised healthcare guidelines due to differing symptoms and treatment processes for each rare disease can present challenges to communications (Hannemann-Weber et al., 2011).

Increasingly social media and the internet are used as communication platforms to engage with the rare disease community (Black and Baker, 2011; Milne and Ni, 2017; Pogue et al., 2018; Price, 2016; Sarasohn-Kahn, 2008; Zhu et al., 2018). Social media and the internet has been associated with a number of communication challenges including the potential sharing of low-quality and inaccurate information (Milne and Ni, 2017; Price, 2016; Sarasohn-Kahn, 2008; Zhu et al., 2018). Other challenges are around privacy, regulation, policy, limited demographic representation, potential unbalanced information and an inability to review content (Milne and Ni, 2017; Pogue et al., 2018; Sarasohn-Kahn, 2008).

Rare disease patient registries allow for the collection of high quality patient data, drug evaluation, pharmacovigilence, and clinical trial recruitment, providing a platform of information and communications for rare diseases (Ambrosini et al., 2018; Lochmüller et al., 2017). Challenges such as maintenance, keeping updated records, data anonymisation and ownership, accessibility, interoperability, regulation constraints and an absence of standardised registries can impede communications, with many registries lacking harmonisation and

sustainability (Ambrosini et al., 2018; Bellgard et al., 2017; Cavero-Carbonell et al., 2016; Lochmüller et al., 2017; Mulberg et al., 2019; Pearson et al., 2018).

Whilst there are a number of rare disease registries that can aid in the communications around rare disease, it has been found that there are few orphan drug specific databases, with registries lacking data on alternative orphan drug treatments that may be available (Bellgard et al., 2017; Giannuzzi et al., 2017; Pearson et al., 2018). Although the orphanet database provides information on orphan drugs, this can be limited (Bellgard et al., 2017; Giannuzzi et al., 2017).

There are many challenges to communications around rare diseases and orphan drugs, this can lead to negative outcomes and inadequate management and engagement with the rare disease community (AMICULUM, 2014; Benjamin et al., 2017; Blay et al., 2016; Budych et al., 2012; Evans, 2018; Giannuzzi et al., 2017; Hannemann-Weber et al., 2011; Hansen, 2012; Limb et al., 2010; Liuccio et al., 2015; Pearson et al., 2018; Price, 2016; Raffai and Timmis, 2017; Urwin et al., 2016).

Communication strategies and relevant theories

Bi-directional models of communications state that communications should not be a unidirectional flow of information that is 'broadcast' to target audiences (AMICULUM, 2014; Charles, 2014). In healthcare communications, traditionally information would be 'broadcast' from a pharmaceutical company to a HCP and patient (AMICULUM, 2014; Lee and Garvin, 2003; Trench, 2008).

In healthcare communications this unidirectional model is often described as the 'deficit model' or 'medical model' of communications, where information is communicated in a one-way flow by experts (HCPs) to audiences (patients) assumed to be deficient in understanding (Joubert, 2014; Lee and Garvin, 2003; Trench, 2008). Audiences are seen as ignorant, waiting for information to be presented to them (Joubert, 2014; Lee and Garvin, 2003; Trench, 2008). In this view, communications are a monologue where information is transferred to patients with the hope that health behaviours might change (Lee and Garvin, 2003; Trench, 2008). There is a focus on individualism, where the patient is solely responsible for their own health (Lee and Garvin, 2003). Expertise from HCPs is assumed over lay persons, ignoring their knowledge and perspectives (Lee and Garvin, 2003; Trench, 2008). This is seen as taking a technocratic or top-down view of communications where experts are gatekeepers of information (Joubert, 2014; Trench, 2008).

This model has been criticised for not taking into account the different needs and views of a target audience, assuming audiences may not understand a given topic (Joubert, 2014; Trench, 2008).

The Bi-directional model of communications is often described as the dialogue model where information is communicated in a two-way flow between experts and audiences, taking into account their different needs and experiences (AMICULUM, 2014; Joubert, 2014; Trench, 2008). This takes a bottom-up approach to communications (Trench, 2008).

The dialogue model has been described in different contexts in the field of science communication, including in the interactive and engagement model (Joubert, 2014; Trench, 2008).

In the interactive model of communications, contextual factors influence the way the public views science, with a two-way flow of information between experts and audiences (Joubert, 2014; Trench, 2008). The engagement model builds on this, with dialogue and interaction between experts and publics, involving direct input from audiences in shaping decisions and influencing communications (Joubert, 2014; Trench, 2008).
In healthcare communications, this involves the movement of communications from simple information transfer to information exchange with all stakeholders (Lee and Garvin, 2003). Based on this principle, it has been argued that the power of communications should shift from

experts and HCPs to all stakeholders, especially the patient (Joubert, 2014; Lee and Garvin, 2003).

The rare disease network is complex, involving input from multiple stakeholders across the patient pathway communicating in collaborations and partnerships (AMICULUM, 2014; Levinson, 2019). Due to this, bi-directional communications involving all stakeholders including HCPs, patients, families and patient advocacy groups are vital to ensure the success of communications (AMICULUM, 2014; Levinson, 2019).

This has been shown in patient community partnerships utilising web platforms to collect data and assess the needs of patients living with congenital hypogonadotropic hypogonadism (CHH), providing a bi-directional flow of information, allowing patients to be connected with HCPs (Dwyer et al., 2014). Other examples of bi-directional communications include patient-physician relationships where shared decision making has been utilised, acknowledging the patient as an active partner in information exchange and the healthcare decision making process (Budych et al., 2012; Hannemann-Weber et al., 2011).

The dialogue model has been used as the basis in the development of innovative and collaborative partnerships involving the global atypical haemolytic uraemic syndrome (aHUS) patient registry and aHUS alliance (Abma and Broerse, 2010a; Woodward et al., 2016). The dialogue model

being used to construct effective partnerships, involving a number of key stages to facilitate their effective development (Abma and Broerse, 2010a; Woodward et al., 2016). The overall aim to support patient centred care and the development of new treatments (Woodward et al., 2016).

Based on these communication theories a number of key principles for effective communications have been suggested (Joubert, 2014). These include accessibility, relevance, focus, style, emotion and starting at the end (Joubert, 2014). In the context of healthcare communications, accessibility would describe how the needs of the patients and stakeholders should be taken into account (Cooke et al., 2017; Joubert, 2014). The information that is communicated should be relevant to the stakeholders and patient being targeted, with a clear focus on the key messages to be communicated (Cooke et al., 2017; Joubert, 2014). The style of communications should be jargon free and easy to understand (Joubert, 2014; Sharon and Baram-Tsabari, 2014). Emotion is important in communications, with emotive communications with a clear narrative more likely to engage with patients and stakeholders then just presenting large volumes of data or information (Goetghebeur et al., 2017; Joubert, 2014; Torres and Pruim, 2019). Communications should also start at the end with the implications and potential benefits of an orphan drug being presented before methods and data (Goetghebeur et al., 2017; Joubert, 2014).

Other communication theories that can be applied to rare disease communications include the uses and gratification theory, explaining the motivation to consume and share content (Walker, 2012; Zhu et al., 2018). This has been exemplified by patients with alpha-1 antitrypsin deficiency (AATD) and their evaluation of the National Institute of Health (NIH) AATD specific website and in health seeking behaviours (Walker, 2012; Zhu et al., 2018).

The principles of uses and gratification theory (UGT) state that cognitive motivations influence perception, behaviours and the interpretation and evaluation of information (Blumler and Katz, 1974; Zhu et al., 2018). There are a number of important principles of UGT including surveillance and enjoyment motivations, influencing how patients seek information (Blumler and Katz, 1974; So, 2012; Zhu et al., 2018). Surveillance describes the desire to accurately understand an issue and enjoyment describes the desire to maintain a positive mood when consuming information (Blumler and Katz, 1974; So, 2012; Zhu et al., 2018). Gratifications are achieved when motivations are satisfied by sources and the content of communications (Blumler and Katz, 1974; Zhu et al., 2018). In the context of AATD and the evaluation of the NIH website the completeness, quality, interest and design were important in achieving gratification (Zhu et al., 2018).

Information completeness describes the authority and comprehensiveness of information linked to a specific health condition (Dutta-Bergman, 2004; Tustin, 2010; Zhu et al., 2018). The quality of information is also important for gratification, with higher quality information leading to gratification, helping to reduce the potential uncertainty of information read by patients (Zhu et al., 2018). Both information completeness and quality maintain surveillance motivations (Zhu et al., 2018).

The interest of content and sources of information are important, with information that facilitates learning and education increasing the enjoyment motivation of patients (Berger, 2014; Zhu et al., 2018). Content that is user-friendly is also important to maintain the enjoyment motivation of content and sources (Braddy et al., 2008; Zhu et al., 2018). This study highlighted how applying UGT can increase the effectiveness of content and sources of communications in the design of a patient website (Zhu et al., 2018).

Critical review

The unmet needs of the rare disease patient in relation to orphan drugs provides a great opportunity for innovation in communications to ensure their success (Darrow et al., 2018; Hansen, 2012; Melnikova, 2012; Schieppati et al., 2008). In the next few years there will be an increase in orphan drugs for both rare oncology and non-oncology conditions (Alliance for Regenerative Medicine, 2019; Evaluate, 2019; Melnikova, 2012; Wellman-Labadie and Zhou, 2010). This will revolutionise the treatment of rare diseases, making it even more important that once these drugs come to market that communications are effective and innovative, allowing for the continuation of treatment during the post-commercial or marketing phase. (Alliance for Regenerative Medicine, 2019; Darrow et al., 2018; Evaluate, 2019; Melnikova, 2012; Wellman-Labadie and Zhou, 2010). This will involve real world data collection, understanding the whole patient pathway, collaboration of all stakeholders and creative communications that utilise a multi-media approach that is truly patient centric (AMICULUM, 2014; Benjamin et al., 2017; Black and Baker, 2011; Blay et al., 2016; Charles, 2014; Cooke et al., 2017; Hansen, 2012; Jiménez et al., 2018; Joubert, 2014; Julkowska et al., 2017; Kuehne et al., 2014; Levinson, 2019; Lochmüller et al., 2017; Milne and Ni, 2017; Morel and Cano, 2017; Mulberg et al., 2019; Pogue et al., 2018; Raffai and Timmis, 2017; Tamí-Maury et al., 2017; Tozzi et al., 2013).

Using the healthcare communications company Open Health as a case study, this project aims to critically assess the current landscape and future directions of communications in relation to the post-commercial launch of orphan drugs to treat rare diseases. This will occur via the thematic analysis of articles, opinion pieces and semi-structured interviews conducted at Open Health. Conducting this critical review will inform current practice, stimulate discussion and help to improve the communication of complex scientific information about rare diseases and orphan drugs for the benefit of the patient.

Methods

This project focused on a qualitative approach utilising a combined thematic analysis of both secondary (articles) and primary (interview) data, using publically available articles from Open Health and interviews with directors and CEOs across Open Health. Thematic analysis is a qualitative approach that looks to analyse and reveal themes within data, organising and describing data in detail (Braun et al., 2018; Braun and Clarke, 2006; Tuckett, 2005; Vaismoradi et al., 2016). This approach was taken as it allows for greater flexibility compared to other qualitative approaches including strict grounded theory (Braun et al., 2018; Braun and Clarke, 2006; Hallberg, 2006; Tuckett, 2005). Themes were identified using a semantic approach to reveal the basic meaning and key points from the data (Braun et al., 2018; Braun and Clarke, 2006). Initial identification of themes moved from a basic description of the data to a broader interpretation of themes, placed into their wider context based on the relevant literature (Braun et al., 2018; Braun and Clarke, 2006; Vaismoradi et al., 2016).

Search strategy

The search strategy for this critical review is shown in Figure 1.

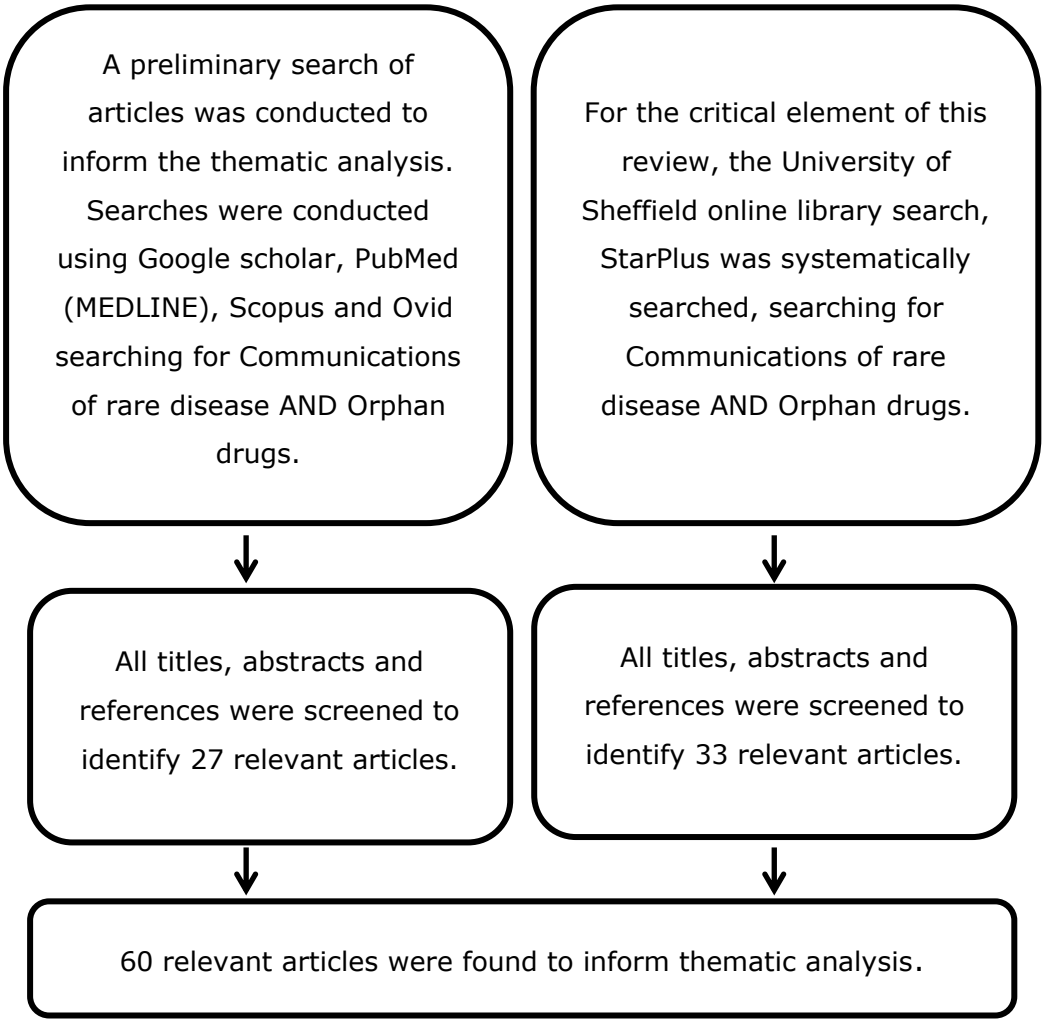

Figure 1 - Search strategy for critical review. A preliminary search of articles was conducted to inform the introduction, conclusion and thematic analysis. Searches were conducted using Google scholar, PubMed (MEDLINE), Scopus and Ovid searching for *Communications of rare disease AND Orphan drugs*. All titles, abstracts and references were screened to identify 33 relevant articles. For the critical element of this review, the University of Sheffield online library search, StarPlus was searched. The key search terms used were 'Communication', 'Rare Disease' and 'Orphan drug' with the overall search *Communications of rare disease AND Orphan drugs*. These articles were limited to humans, peer-reviewed-articles, reviews and books between the years 2016 to 2019. Titles and abstracts were screened to identify 27 relevant articles. Additional literature was found during thematic analysis and to inform the methods, with relevant reading and reports suggested by Open Health.

Articles and opinion pieces

Thematic analysis was conducted of 54 publically available opinion pieces and articles from the Open Health website (Open Health, 2019) in relation to communications, challenges to communications, future directions to communications, patient and stakeholder engagement, orphan drugs, real-world evidence and data, post-market authorisation, strategy and plan, health technology, health technology assessments and the post-commercial launch of orphan drugs. Articles and opinion pieces analysed were archived back until 2014. These articles and opinion pieces generally or specifically spoke about rare diseases, or were more generally related and relevant to communications and patient engagement. All articles and opinion pieces talked about important aspects to communications, which were deemed relevant for analysis as communications do not occur in isolation and are not only a rare disease issue. Titles of articles were screened and deemed relevant based on the topic areas listed above, identifying 54 articles for analysis dating back to 2014. If it was not clear from titles if the articles were relevant, articles were read and deemed relevant if they spoke about the areas listed above.

Interviews

To further inform thematic analysis with regards to communications about the post-commercialisation of orphan drugs, five 10-30 minute semi-structured interviews were conducted. Interviews were conducted with five experts, senior individuals and directors within Open Health, conducted at their London offices between 9/7/2019 to 26/7/2019. Participants were identified using purposive sampling based on recommendations from the director of rare diseases within Open Health and approached for interviews. All participants were sent participant information sheets, consent forms and an interview schedule prior to the interview. An interview schedule was written based on the research questions, informed by input from reading and the thematic analysis of articles.

For example from reading, *Building the patient community* a number of challenges to the rare disease community were highlighted (Raffai and Timmis, 2017). This informed this line of questioning in relation to challenges:

In your opinion what areas of communications need to be improved in relation to the post-commercial launch of an orphan drug?

Questions covered two main areas. These two areas were current practice and future directions in relation to the post-commercial launch of an orphan drug.

Interviews were recorded using a Dictaphone (Olympus DM-670, Tokyo, Japan) with interview transcripts analysed verbatim via thematic analysis using the qualitative analysis software NVivo 12 (QSR international, Melbourne, Australia).

Data analysis

Data was analysed using the qualitative analysis software NVivo 12. Utilising NVivo 12, an inductive, data-driven approach to coding was taken based on reading, interviews and interpretation of opinion pieces and articles (Braun and Clarke, 2006; Fox, 2008). Thematic analysis taking an exploratory approach, using Open Health as a case study revealed a number of themes (nodes) (Braun et al., 2018; Braun and Clarke, 2006). These themes were organised into a superordinate and subordinate hierarchy.

Coding strategy and process of thematic analysis. To process the data for coding, articles and opinion pieces were imported as PDF

documents. PDF documents were analysed first followed by interview transcripts that were imported as documents into Nvivo 12.

Themes in relation to communications were highlighted from textual data (articles, opinion pieces) taking an iterative approach, with themes emerging, developing and changing as data were analysed (Bassett, 2012; Marshall, 1996). The coding of data was informed by the literature, aims and the research question in relation to communications in rare disease and orphan drugs. The literature highlighted important areas and challenges for rare disease communications and orphan drugs around orphan drug initiatives, rare disease registries, rare disease patient outcomes, regulatory processes, social media use in rare disease research, the rare disease patient and rare disease community. This helped to inform the identification of both superordinate and subordinate themes.

Initial superordinate and subordinate themes were identified as the data were coded, with common themes identified across other articles and opinion pieces. New themes emerged as coding took place. Throughout the process data was revisited. This same process then took place for interview transcripts with common themes found with articles and opinion pieces.

Once all the data had been coded, a process of refinement, re-coding and reorganisation organised themes into distinct groups of superordinate

themes relating to communications. These distinct groups of superordinate themes were organised into a hierarchical structure with subordinate themes nested within them. A worked example is shown in Table 1.

Table 1

Worked example of textual coding from Article 1, showing initial code and final code assigned.

Text	Initial code	Final code
'Companies can also help produce ***practical materials*** that summarise key information in a succinct way, to serve as a reference for instructing physicians on how to manage or refer patients as appropriate.' (Article 1)	The code '***practical materials***' was assigned.	Upon further analysis a number of other platforms and media for communications where highlighted including digital apps, video abstracts, and animations and visuals. Originally these were coded at their own distinct nodes. Upon refinement and reorganisation of nodes, these individual codes where merged into one subordinate theme of communication media and platforms within the superordinate theme of communications.

Trustworthiness of analysis. To ensure the trustworthiness of thematic analysis, the trustworthiness criteria proposed by Lincoln and Guba (1985) was used to guide the analysis as much as possible, following the principles of credibility, transferability, dependability and conformability (Korstjens and Moser, 2018; Lincoln and Guba, 1985; Nowell et al., 2017).

Credibility was ensured with prolonged engagement with the literature, data and insight provided during the Open Health placement (Korstjens and Moser, 2018; Lincoln and Guba, 1985).

Transferability occurred with a clear and relatively detailed description of each superordinate and subordinate theme (Korstjens and Moser, 2018; Lincoln and Guba, 1985).

Although no audit occurred, data was processed logically article by article with a partial diary kept. Records of transcripts and articles were kept as textual data. Notes, memos and a description of each theme were written and a concept map drawn to keep track of developing themes. This helped to ensure dependability, confirmability and reflexivity of analysis (Korstjens and Moser, 2018; Lincoln and Guba, 1985).

Ethical approval

Ethical approval was obtained on 9/07/2018 from The University of Sheffield UREC (University Research Ethics Committee) under the department of Animal and Plant science ethics sub-committee.

Results and Discussion

In total six superordinate themes were identified based on thematic analysis of 54 publically available articles and opinion pieces obtained from the Open Health website and five interviews conducted. These six superordinate themes were: communications, challenges, information, data and evidence, strategy, plan and launch, patients and stakeholders, and future directions. These Superordinate themes had further subordinate themes nested within them as described below (See Table 2 for superordinate themes and subordinate themes).

Communications had three subordinate themes including communication media and platforms, digital communication, and message content and delivery.

Challenges had nine subordinate themes including awareness, disconnected, economics, global, healthcare ecosystem, data and evidence, orphan therapies, and patients.

Information, Data and evidence had four subordinate themes including big data, evidence, transparency, and real-world evidence and value propositions.

Strategy, plan and launch had two subordinate themes including collaboration and partnerships, and regulation, policy, guidance and initiatives.

Patients and stakeholders had five subordinate themes including co-creation, connectivity, education and networking, patient needs, and stakeholders and experts.

Future directions had three subordinate themes including collaboration, data and evidence, and framework and system.

All superordinate and subordinate themes were relevant and important for communications (or similar) of rare diseases and orphan drugs, with the mapping of superordinate and subordinate themes shown in Figure 2.

Table 2

Superordinate themes and subordinate themes developed during thematic analysis of articles, opinion pieces and interviews**,** with topics included in some of the subordinate themes shown in italics.

Superordinate theme	Subordinate theme
Communications	• **Communication media and platforms** • **Digital communication** • **Message, content and delivery:** *behaviour, centralised, content and messaging, engagement, global approach, multi-channel, personalised, transparent*
Challenges	• **Awareness** • **Disconnected** • **Economics** • **Global** • **Healthcare ecosystem** • **Data and evidence** • **Media** • **Orphan therapies** • **Patients**
Information, data and evidence	• **Big data** • **Evidence** • **Transparency** • **Real-world evidence and value propositions**
Strategy, Plan and Launch	• **Collaboration and partnerships** • **Regulation, policy, guidance and initiatives**
Patients and Stakeholders	• **Co-creation** • **Connectivity** • **Education and networking** • **Patient needs:** *patient engagement, patient groups, patient pathways, patient-centricity* • **Stakeholders and experts**
Future directions	• **Collaboration** • **Data and evidence** • **Framework and system**

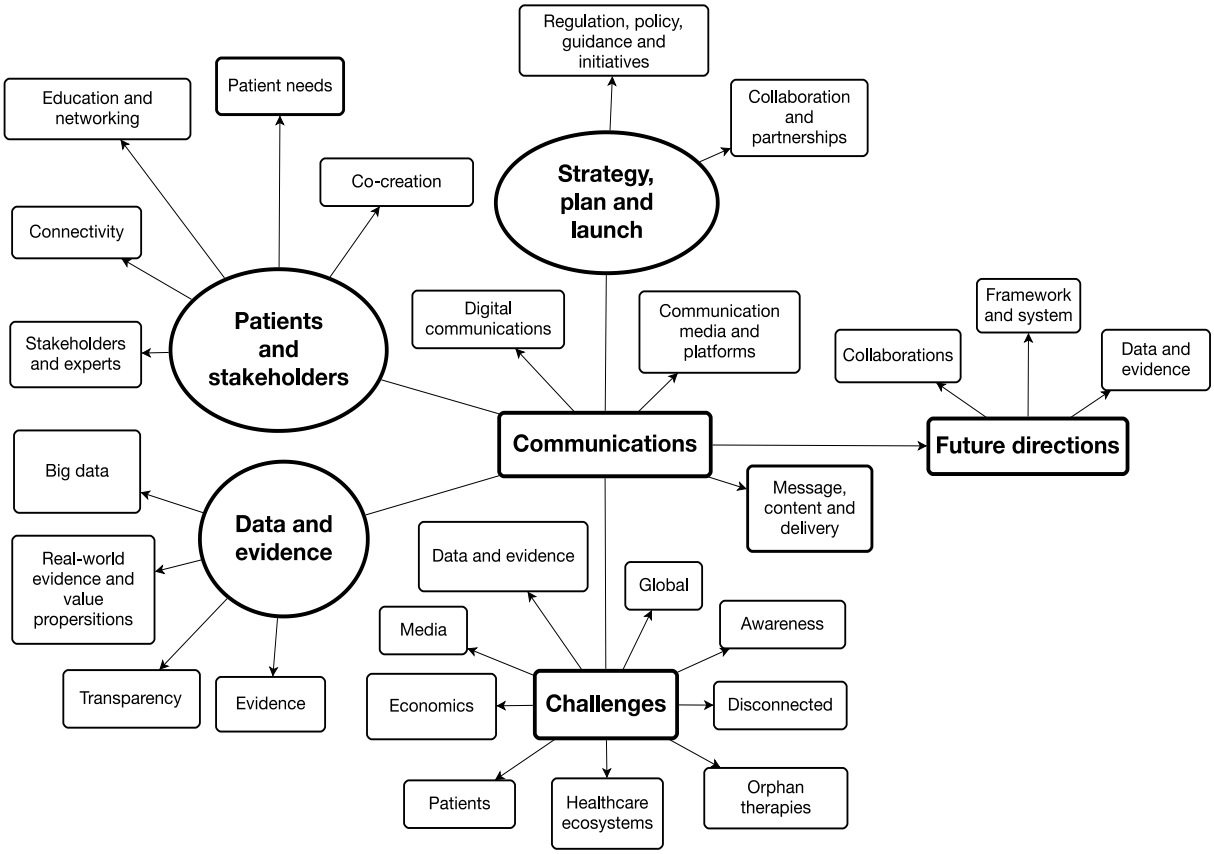

Figure 2 – Thematic mapping showing the six superordinate themes with subordinate themes nested within them. Communications are of central importance with four superordinate themes: challenges, patients and stakeholders, data and evidence, and strategy, plan and launch with bidirectional associations with communications, leading to the final theme of future directions.

Communications

This superordinate theme discussed *communication media and platforms*, how they might be utilised to improve communications and what is currently being done. The use of *digital communications* was also discussed.

Communication media and platforms. The different media platforms for communications were discussed in the texts and interviews. The communications platforms highlighted from this thematic analysis included digital apps, video games and gamification, video abstracts, animations and visuals, journals, disease registries, hubs and meetings, some of which are exemplified below.

"Gamification. We can utilise the powerful systems central to games to non-game applications, vastly improving engagement." (Article 30)

"…visual standpoints that supplements the primary data driven article." (Interview 3)

"…inspection of each journal's Instructions to Authors will usually reveal the right journal and the correct medium (eg, plain text, audio, graphic illustration, or video or other digital) to accurately communicate research findings to the medical specialist and lay audience." (Article 40)

"…creation of disease registries to support further understanding of the disease…" (Article 18)

"…more platforms that people could go on to learn more about the condition that they can network…So I do think some kind of hub set up..." (Interview 1)

"…it's important to have a presence at those local meetings as well, because a lot of those physicians don't have the means to get to the large international meetings." (Interview 3)

Discussions in the literature support communications that use a variety of media and platforms including meetings and symposiums, registries and visuals (infographics) to ensure communications have a broad reach (Ambrosini et al., 2018; AMICULUM, 2014; Bellgard et al., 2017; Blay et al., 2016; Goetghebeur et al., 2017; Lochmüller et al., 2017; Mulberg et al., 2019; Woodward et al., 2016). This has been shown to be important in the development of patient-centred outcome measures, with the greater number of communication channels used leading to the development of better communication models and strategies (Morel and Cano, 2017). Others have raised concerns about overcomplicating communications by using too many channels, instead advocating for a more targeted approach to communications (AMICULUM, 2014; Cooke et al., 2017; Levinson, 2019).

This is supported by the wider science communication literature where using diverse communication media and platforms are important for effective communications to different audiences (Cooke et al., 2017; Joubert, 2014; Kuehne et al., 2014).

Social media was discussed as a communication platform in its potential to engage, educate and provide information to patients.

"Pharmaceutical companies can use social media to engage and educate patients, as well as provide reliable information about their products." (Article 4)

Social media was discussed in a positive light and is supported by the literature, where social media has been described as providing a source of big data that could be used to obtain information for pharmacovigilance, orphan drug development, HCP education and patient advocacy (Black and Baker, 2011; Milne and Ni, 2017; Pogue et al., 2018; Price, 2016; Sarasohn-Kahn, 2008; Schumacher et al., 2014; Walker, 2013). Although a number have raised concerns of the use of social media in communications, particularly in terms of issues around data privacy and how to ensure the quality of data (Black and Baker, 2011; Milne and Ni, 2017; Pogue et al., 2018; Sarasohn-Kahn, 2008)

The need to summarise and communicate information in an easy to understand and simple way to lay audiences was seen as important for communications.

"Companies can also help produce practical materials that summarise key information in a succinct way..." (Article 1)

This has been discussed in the literature as being important when trying to communicate complex information to lay-audiences (AMICULUM, 2014; Baur and Prue, 2014; Cooke et al., 2017; Joubert, 2014).

Digital communication. The importance of digital communication, therapeutics, technology and online platforms was expressed in the text and interviews, revealing that digital communications, online communities and the internet are important for communications and could improve communications for rare diseases, patients and orphan drugs. Articles discussed the use of digital communications in terms of virtual online communities and the use of online learning platforms.

"…'virtual multidisciplinary teams (MDTs)' are often a way of bringing together both experts and interested HCPs…Online learning platforms with interactive and engaging content can quickly provide audiences with key information…" (Article 1)

"…online communities are playing a vital role in connecting those living with rare cancers together." (Article 48)

Digital technologies and channels were described as providing an opportunity for customer-centric experiences and enhancing communications with patients.

"…companies need to ensure that they utilise digital technologies and multichannel opportunities…to ensure a positive and customer-centric experience." (Article 43)

"…harnessing digital channels to expand communications with patients…" (Article 47)

One of the interviews described the use of online communities in connecting patients with rare diseases and providing information about drug treatment, emphasising the importance of virtual communities.

"…virtual communities, virtual working groups, virtual discussion forums I think is gonna be the big growth area in rare disease." (Interview 4)

The importance of virtual communities and online learning platforms for communications in rare disease and orphan drugs has been discussed in the literature (Al-Jasmi et al., 2010; Dwyer et al., 2014; Julkowska et al., 2017; Pogue et al., 2018; Tamí-Maury et al., 2017; Tozzi et al., 2013). Virtual communities have been discussed in the context of European Reference Networks (ERNs) for rare diseases (Julkowska et al., 2017). ERNs allow for HCPs to connect via virtual networks to share expertise and knowledge, with the aim of improving patient outcomes and rare disease research (Julkowska et al., 2017). Virtual communities have also been implicated in community-based participatory research, helping to overcome geographical barriers and improve accessibility of communications (Tamí-Maury et al., 2017). Online learning platforms and web-based needs assessments have been shown to be important for education and support in rare diseases (Al-Jasmi et al., 2010; Dwyer et al., 2014)

Patient forums, such as patients like me have been shown to be important, allowing patients with different diseases to share information online (Pogue et al., 2018). Online databases and portals have also been shown to be important for communications, for example Orphanet, providing information on rare disease and orphan drugs (Lynn et al., 2017; Pogue et al., 2018).

The use of the internet has been shown to be important for communications in terms of providing information about rare diseases and/or orphan drugs (Black and Baker, 2011; Bouwman et al., 2010; Morgan et al., 2014; Tozzi et al., 2013; Zhu et al., 2018).

In one of the interviews, the importance of different digital tools was highlighted, with the use of Artificial Intelligence (AI) discussed.

"Keeping those patients engaged and interactive with the registry and you know well over many years in some cases is really important. So there are a lot of different digital tools for doing that that are coming into play. And AI it's going to be very important in that area." (Interview 3)

The use of digital tools has been discussed in the literature as a way to improve communications, using mobile tools and biosensors to obtain data that could be used to monitor patients for potential adverse drug reactions (ADRs), collecting constant data that could be linked to patient databases and registries (Pogue et al., 2018; Price, 2016). Whilst AI has not be directly discussed, a number of authors have suggested that novel analytical techniques are required to assist in assessing the efficacy and safety of orphan drug treatments and ADRs (Mulberg et al., 2019; Price, 2016).

Digital communications were also discussed in the context of a 'digital revolution', providing innovative and new channels of communicating content.

"The digital revolution has opened many additional channels for the dissemination of customized content…gaining insights into the way in which target stakeholders prefer to receive their information." (Article 29)

The importance of digital communications has been discussed in the science and healthcare communication literature, with online media changing the communication landscape and providing new communication opportunities (Burke-Garcia and Scally, 2014; Dudo, 2015; Joubert, 2014; Stones and Smith, 2018; Trench, 2008).

Message, Content and delivery. This subordinate theme discussed important aspects to the message, content and delivery of communications including behaviour, centralised, content and messaging, engagement, global, multi-channel, personalised, and transparent.

Behaviour. Emotional resonance in patient support programs was discussed. This relates to communications in rare diseases and orphan drugs, as without taking behaviour into account it was suggested that modifying patient behaviour and improving patient outcomes would be more challenging.

"…if your patient support programme doesn't have a real emotional resonance with the user then it will not be possible to modify behaviour and deliver improved clinical outcomes." (Article 30)

Emotions, behaviours and contextual factors are important for communications and drive how patients interact with content (Gasiorek, 2018; Joubert, 2014; Schumacher et al., 2014; Zhu et al., 2018). This is supported by communications theory including uses and gratification theory, stating that patients will select media if it satisfies a number of gratifications, including surveillance and enjoyment motivations (Schumacher et al., 2014; Zhu et al., 2018). Traditional communication theory emphasises the importance of behaviours, cognitive representations and contextual factors in communications (Gasiorek, 2018, 2018; Joubert, 2014; Schumacher et al., 2014; Zhu et al., 2018). This can be explained by the code model of communications and the interactive communication model (Gasiorek, 2018; Joubert, 2014).

Centralised. Having a centralised approach was discussed as making communications easier and allowing all stakeholders to access information in one place. This was discussed as involving a coordinated and integrated approach that can be put into context across the whole patient pathway.

"Connecting healthcare professionals (HCPs), the delivery channel, carers and the patient through one seamless ecosystem can start to break down silos in patient management and drive improvements in patient care." (Article 47)

"…having somewhere central that people can go to and find the information." (Interview 1)

"…increase the basis of understanding I think and that will probably require a coordinated approach of many stakeholders…" (Interview 1)

"…good communications is about putting it in context, so I think that's really really important…" (Interview 1)

This has been highlighted in the literature with the importance of research consortia in centralising collaborations in rare disease research discussed (Julkowska et al., 2017; Lochmüller et al., 2017). Discussions were also around creating centralised patient registries and stores of knowledge about rare diseases that could be easily accessed and shared (Raffai and Timmis, 2017; Torrent-Farnell et al., 2018) The importance of the integration and context of patient information and outcomes was discussed as being important in the development of patient reported outcomes, patient diagnosis and care (Morel and Cano, 2017; Pogue et al., 2018; Urwin et al., 2016). Others have discussed increasing integration

between the EMA and FDA in orphan drug marketing approvals and processes (Giannuzzi et al., 2017).

The importance of providing context has been discussed in science communication models, including the contextual model where audiences respond to information based on environmental and psychological schemas (Gasiorek, 2018; Joubert, 2014; Lee and Garvin, 2003; Trench, 2008).

Content and messaging. Content and messaging was seen as important to communications. This should be simple, impactful, and memorable, with a narrative and consistent messaging for the stakeholder.

"…ensuring that content is memorable, engaging and leaves the audience with key messages…" (Article 1)

"Messaging needs to be simple." (Article 39)

"Creating impactful communications…will assist in informed decision making through health technology assessments…" (Article 50)

"Sharing experiences in rare cancer and simply explaining to others how their lives have changed is arguably the most effective way for patients to generate awareness…" (Article 48)

"Communications should address the needs of a broad range of clinical and payer stakeholders, with consistent messaging…" (Article 3)

Content and messaging are important in science communication, with clear narratives allowing for effective communications (Cooke et al., 2017; Joubert, 2014) This has been discussed as being a way to improve value assessments in HTA processes (Goetghebeur et al., 2017). Narratives are also important in creating impactful content (AMICULUM, 2014; Joubert, 2014; National Academies of Sciences, Engineering, and Medicine (U.S.), 2017). Content and messaging that is high quality and accurate has been discussed in the use of social media for orphan drug development and its importance to communicate with patients and stakeholders (Milne and Ni, 2017). Clear messaging of content is also important in ensuring rare disease patients can make informed health decisions, promoting patient self-advocacy (Liuccio et al., 2015).

The timeliness of the delivery of the content and messaging of information was seen as vital to ensure all stakeholders can be effectively communicated with. This has been discussed in the context of providing information before strong views have been formed that could be hard to change and prevent effective communications (Bruine de Bruin and Wong-Parodi, 2014; National Academies of Sciences, Engineering, and Medicine (U.S.), 2017).

"…it's really important to get the information out in as timely as a manner as you can. So when the clinical trials are done, you don't want to cause another delay of one year before the physicians are getting information about this data…" (Interview 3)

Engagement. Analysis suggested that communications should involve the engagement of stakeholders early in the process of healthcare ecosystems, patient pathways and drug development. This engagement was discussed as involving a clear dialogue that communicates with the whole patient community, taking a holistic approach.

"…dialogue in the public domain is really important because, patients and advocacy groups in rare disease are certainly, should be seen as…a critical stakeholder in that communications." (Interview 2)

"…improving communications in rare disease is very much related to ensuring that the rare disease community is seen as one." (Interview 2)

Engagement and dialogue with all stakeholders should be central to communications as has been discussed in the literature, in engaging with rare disease patient populations via social media and partnerships for research, clinical trial recruitment, patient support and advocacy (AMICULUM, 2014; Charles, 2014; Milne and Ni, 2017; Sarasohn-Kahn,

2008; Schumacher et al., 2014; Torrent-Farnell et al., 2018; Woodward et al., 2016). A lack of high quality information about rare diseases has been found to be a challenge to patient engagement (Zhu et al., 2018). Other science communication literature has highlighted the importance of engagement in communications (Cooke et al., 2017; Joubert, 2014; National Academies of Sciences, Engineering, and Medicine (U.S.), 2017; Trench, 2008; Wilsdon et al., 2004).

Global approach. Having a flexible global approach to communication strategies was seen as important to reach all countries and meet the different needs of the different global healthcare systems.

"Communications strategies developed at global level should take into account the similarities and differences between global healthcare systems…individual countries will need some flexibility within the global communications strategy to address regional and local differences between markets." (Article 3)

This has been highlighted in the literature as different countries have different healthcare systems that could affect communication strategies, with regional differences making flexible communications important (Cavero-Carbonell et al., 2016; Darrow et al., 2018; Giannuzzi et al., 2017; Jiménez et al., 2018; Julkowska et al., 2017; Lampert et al., 2016;

Lochmüller et al., 2017; Lynn et al., 2017; Mulberg et al., 2019; Torrent-Farnell et al., 2018).

Multi-channel. It was suggested that having a multi channel communications approach was important to ensure effective communications and a wide stakeholder reach. Varied approaches to communication were seen as important in improving communications and getting information out about rare diseases and orphan drugs.

"…you really need to make sure that you're addressing all those different channels of information and getting it out there…" (Interview 3)

"…it can be difficult for rare cancer patients to get their voice heard, many patients are proactive in communicating across multiple media channels…" (Article 48)

This is backed up by the literature discussing the importance of multi-channel approaches to communications, allowing for a wider and varied communications reach (AMICULUM, 2014; Cooke et al., 2017; Joubert, 2014; Kuehne et al., 2014).

Personalised. The importance of having a personalised communications approach to each patient and patient group was seen as important for communications.

"…with rare disease, I think making it far more personalised, making it very much more specific as well…" (Interview 4)

"…we need to offer something of value and create relevant and personalised communications…" (Article 16)

This is discussed as being important in the literature, taking the needs of the individual rare disease patient and groups into account, to ensure communications across the patient pathway and orphan drug value assessments are patient appropriate (AMICULUM, 2014; Charles, 2014; Hannemann-Weber et al., 2011; Levinson, 2019; Lochmüller et al., 2017; Morel and Cano, 2017; Pearson et al., 2018; Raffai and Timmis, 2017; Zhu et al., 2018).

Transparent. Transparent and honest communications were seen as being important, involving pharmaceutical companies being proactive in their communications with healthcare systems as discussed by some of the interviews below.

"…honest communication about what is available to spend, but also an in detailed understanding of what these diseases actually are and what the impact is on the patient…" (Interview 1)

"Bluebird I think have been very proactive in their communications with health systems." (Interview 2)

"…just good communication practice standpoint in this area, it's data transparency…" (Interview 3)

Within the literature conversation around transparency is generally in relation to data, social media, drug access and diagnosis (Charles, 2014; Goetghebeur et al., 2017; Huyard, 2009; Lochmüller et al., 2017; Milne and Ni, 2017). More broadly speaking about the importance of honesty and openness in communications in the interaction of pharmaceutical companies with regulatory bodies and patient advocacy groups (AMICULUM, 2014; Blay et al., 2016; Hansen, 2012). Honesty has also been shown to be important for science communications as effective communications are built around trust (Cooke et al., 2017; Joubert, 2014).

Challenges

The challenges to effective communications in relation to rare disease, patients and orphan drugs were discussed, as revealed by the subordinate themes below. Some of these challenges have been discussed in the literature.

Awareness. A lack of awareness was seen as being a challenge that can impede communications and is an area that needs to be improved. Communications were seen as important in driving improved awareness to improve the diagnosis and treatment of rare disease patients.

"…communications should drive better awareness and therefore better diagnosis to people with these conditions." (Interview 1)

A lack of awareness of rare diseases consistently came up within the literature as a barrier to communications (Ambrosini et al., 2018; AMICULUM, 2014; Blay et al., 2016; Bouwman et al., 2010; Budych et al., 2012; Liuccio et al., 2015; Lynn et al., 2017; Milne and Ni, 2017; Raffai and Timmis, 2017; Schieppati et al., 2008; Schumacher et al., 2014; Urwin et al., 2016; Walker, 2013).

Disconnected. It was revealed that many communications are poor as they can be disconnected from patients and their needs.

"If there is a disconnect between patients and pharmaceutical companies, it often comes from poor communication." (Article 37)

Whilst disconnected communications in relation to patients and pharmaceutical companies is not directly discussed in the literature, there is discussion around a lack of harmonisation and disconnected patient registries (Cavero-Carbonell et al., 2016; Lochmüller et al., 2017; Mulberg et al., 2019). Patients were discussed as being central to communications, and if they are disconnected this can negatively impact patient outcomes and orphan drug value assessments (Goetghebeur et al., 2017; Raffai and Timmis, 2017). The literature would suggest that disconnected communications can occur if deficit models of communications are used (AMICULUM, 2014; Joubert, 2014; Trench, 2008).

Economics. The affordability of orphan drugs and payer acceptance in developing an effective targeted value proposition was seen as a challenge to rare diseases. Effective communications was seen as being vital to ensure effective dialogue and debate around orphan disease and drug treatment.

"…how we ultimately solve the affordability question…one critical element of that will be driving effective communications across the rare disease community…" (Interview 2)

"…payer acceptance is crucial. And again when you have so few patients, it's hard to build up that adequate dataset to have a very robust evidence based communication platform and communication out there…" (Interview 3)

The literature discusses this in the context of the HTA for orphan drugs and how effective communications will be needed to overcome challenges to these assessments (AMICULUM, 2014; Goetghebeur et al., 2017; Groft, 2013; Hansen, 2012; Jiménez et al., 2018; Lampert et al., 2016; Pearson et al., 2018; Torrent-Farnell et al., 2018)

Global. This subordinate theme discussed how communications occur on a global and regional scale, with cost implications that can make the dissemination of information difficult.

"…getting that information out there, especially around to the different regions around the world that can be very challenging and very costly for the pharmaceutical companies." (Interview 3)

Whilst the literature does not directly discuss global challenges to communications, it does highlight that different countries and regions have different healthcare systems and regulatory requirements that should be taken into account when communicating (AMICULUM, 2014; Cavero-Carbonell et al., 2016; Darrow et al., 2018; Giannuzzi et al., 2017; Hansen, 2012; Jiménez et al., 2018; Julkowska et al., 2017; Lampert et al., 2016; Liuccio et al., 2015; Lochmüller et al., 2017; Lynn et al., 2017; Pinto et al., 2016; Torrent-Farnell et al., 2018; Urwin et al., 2016).

Healthcare ecosystem. Challenges to engage with the whole healthcare ecosystem by all stakeholders was highlighted, with an emphasis on the importance of pharmaceutical companies to interact will all stakeholders.

"…pharma companies need to recognise and interact with the full healthcare ecosystem, understanding which stakeholders to engage with and prioritise their activities accordingly." (Article 43)

Whilst the direct interaction of pharmaceutical companies and stakeholders is not discussed, the importance of interacting with the healthcare ecosystem has been discussed in the literature (AMICULUM, 2014; Blay et al., 2016; Jiménez et al., 2018; Julkowska et al., 2017; Levinson, 2019; Morel and Cano, 2017; Raffai and Timmis, 2017; Urwin et al., 2016).

Data and evidence. This subordinate theme revealed that a lack of data and evidence could hinder communications around rare disease and orphan drugs, with evidence generation being difficult to obtain effectively. A lack of information was also discussed as being a challenge.

"Traditional methods of gathering evidence are seldom available in rare cancers." (Article 49)

"…immature data available at launch, so that is a real challenge in terms of communication. You know how do you communicate when there's insufficient data." (Interview 1)

This is supported in the literature, with a lack of information, evidence and methods of gathering evidence preventing effective communications around rare disease and the HTA of orphan drugs (AMICULUM, 2014; Benjamin et al., 2017; Goetghebeur et al., 2017; Liuccio et al., 2015; Milne and Ni, 2017; Pearson et al., 2018; Zhu et al., 2018). This is also discussed in the context of registries, with issues around data sharing, anonymity and data collection discussed (Lochmüller et al., 2017; Mulberg et al., 2019; Torrent-Farnell et al., 2018). A lack of high quality information can lead to inadequate diagnosis and management of rare disease conditions (AMICULUM, 2014; Benjamin et al., 2017; Liuccio et al., 2015; Milne and Ni, 2017; Price, 2016; Urwin et al., 2016; Walker, 2013; Woodward et al., 2016; Zhu et al., 2018).

Media. This subordinate theme revealed that media presents specific challenges to communications, including sensationalism, social media and multimedia challenges.

"To face the social media and healthcare challenges of today, and continue to provide reliable information from a trusted source at a time when healthcare systems are under great strain, requires a different way of working." (Article 4)

"So I think it's about how difficult and challenging and how much you communicate the science, how much you are sensationalist and how much you need to put the sort of common sense and uncomfortable facts into the argument." (Interview 1)

"…you really need to make sure that you're addressing all those different channels of information and getting it out there…" (Interview 3)

Within the literature there was only reference to challenges in the use of social media in pharmacovigilance, orphan drug development and general rare disease communications, with bad information on social media potentially interfering with effective communications (Black and Baker, 2011; Milne and Ni, 2017; Price, 2016; Sarasohn-Kahn, 2008).

Orphan therapies. This subordinate theme discussed specific challenges to the development of orphan therapies for the patient, including the rapid and ever evolving orphan drug landscape, therapy pathway and mechanism of action.

"…clarifying such complex mechanisms of action while fully describing the benefits and risks associated with these breakthrough therapies presents a unique challenge for communications…" (Article 40)

"…drug development in orphan haematology is currently very dynamic…This causes rapid change in standards of care, treatment paradigms, referral pathways, and patient expectations. Without quick dissemination of the latest data and clinical experience, HCPs can feel out of their depth." (Article 10)

Communication challenges around orphan therapies are discussed in relation to HTA and regulatory processes for the approval of orphan drugs (AMICULUM, 2014; Darrow et al., 2018; Giannuzzi et al., 2017; Goetghebeur et al., 2017; Hansen, 2012; Jiménez et al., 2018; Lampert et al., 2016; Pearson et al., 2018).

Patients. This subordinate theme discussed specific issues and challenges related to patients relevant to communications, including rare disease patients having complex pathways, with a lack of clear pathways being a challenge to communications.

"In rare disease communities there's often limited clinical knowledge about new drugs, making it difficult to benchmark standards of care or existing patient pathways." (Article 49)

"…there's no clear pathway. There's no clear cost effectiveness route to go down at the moment…the development of that pathway is a challenge." (Interview 1)

These challenges to patients are discussed in the literature in relation to patient pathways, treatment options and unclear standards of care that can hamper effective communications to rare disease patients (AMICULUM, 2014; Benjamin et al., 2017; Groft, 2013; Hannemann-Weber et al., 2011; Hansen, 2012; Jiménez et al., 2018; Levinson, 2019; Morel and Cano, 2017; Raffai and Timmis, 2017; Torrent-Farnell et al., 2018; Urwin et al., 2016).

Data and evidence

This superordinate theme revealed the importance of data and evidence to rare disease patients who are populations of small numbers, highlighting that without data and evidence, communications cannot be successful as having adequate evidence determines the success of orphan drugs. The topics discussed included big data, evidence, transparency, and real-world evidence and value propositions.

Big data. Big data was seen as being integral to communications about rare diseases and orphan drugs. The importance of the depth of data reported was also discussed.

"…'Big Data' will also stretch across many aspects of the marketing mix. It will be used to track patient pathways, patient attitudes, segmentation,

personalisation of messaging, clinical trial recruitment, social media communications…" (Article 45)

Specific discussions of the use of big data were limited to using big data, mined from social media for pharmacovigilance of orphan drugs (Price, 2016).

The depth of detail that is reported was discussed in one of the interviews. With the depth of data referring to the detail of data reported.
"…the depth of data that get reported out through these various communications is very important..." (Interview 4)

The depth, detail and quality of patient data is discussed in the literature as being important for helping to inform effective communications (Liuccio et al., 2015; Milne and Ni, 2017; Paul et al., 2010; Pearson et al., 2018; Tamí-Maury et al., 2017; Zhu et al., 2018). This is especially important for patient registries (Ambrosini et al., 2018; Woodward et al., 2016).

Evidence. This subordinate theme discussed an evidence-based communications approach and its importance for payer acceptance of treatments, the value of solutions and the effectiveness of new treatment approaches, helping to improve patient outcomes and save costs.

"…the importance of getting information out there that's as robust as possible and is as high of a level of evidence as possible, because it's really through that evidence…that the payers are able to make their decisions…" (Interview 3)

"One method of engaging stakeholders will be to provide robust evidence that demonstrates that a new approach is effective and that it will improve patient outcomes and save costs…" (Article 32)

Within the literature evidence was found to be important in informing effective communications and the orphan drug approval processes, important when engaging with stakeholders and those making funding decisions about drugs including payers (Ambrosini et al., 2018; Goetghebeur et al., 2017; Jiménez et al., 2018; Morel and Cano, 2017; Mulberg et al., 2019; Raffai and Timmis, 2017; Zhu et al., 2018).

Transparency. Information transparency was discussed as being important, involving communicating all relevant data and making it available in the public domain.

"…there's so much of a need for information and data about these rare diseases and so much of a drive for data transparency…you end up getting out into the public domain just about every piece of data…" (Interview 3)

The literature discusses transparency as important in HTA processes to ensure effective assessments occur and for transparent data processes (Charles, 2014; Goetghebeur et al., 2017).

Real world evidence and value propositions. The role of real world evidence (RWE), outcome data and patient centred-outcomes (PCOs) were discussed as being important for patient specific data and evidence generation, particularly in the context of rare diseases. This was discussed as being important for the post approval process and an orphan drugs value proposition. The potential of RWE was discussed and its importance for commercial communications programs. Outcome data was discussed as important in proving that investment in a therapy will provide value beyond a clinical trial. Being able to demonstrate the clinical relevance of outcomes, orphan drugs and health technology to relevant stakeholders was also discussed.

"Real-world data collection is essential for the ultimate commercialisation of all brands, but this has to be translated into a coherent commercial communications programme…." (Article 45)

"…importance of real world evidence data. So patient registries and other post marketing studies that are done is really important…" (Interview 3)

"Generating on-going outcome data will be incredibly important in providing a positive feedback loop to prove that the investment in new therapies provides value beyond clinical trials." (Article 50)

The importance of RWE and outcome data is discussed in the literature in the context of RWE collection for patient registries, quality-adjusted life year measurements for HTA, developing endpoints that involve RWE data collection and social media tools for collecting data (Ambrosini et al., 2018; Levinson, 2019; Mulberg et al., 2019; Pearson et al., 2018; Torrent-Farnell et al., 2018; Walker, 2013; Woodward et al., 2016).
Value propositions were discussed in the context of RWE determining the value of a product in the long-term and how this is communicated. The value proposition and reimbursement strategy of an orphan drug was discussed and its importance for effective communications.

"…a direct positive impact of RWE on product reimbursement status. RWE needs to be considered as a key component of a product's value proposition." (Article 11)

"…demonstrating that a drug has positive impacts not just from a clinical perspective but also from a patient perspective…So finding ways of demonstrating value over the long-term…." (Interview 2)

However in the literature, the direct contribution of RWE to value propositions was not discussed.

PCOs were discussed as involving overall, individual and quality of life patient-centred data for evidence generation. This was discussed as being important for rare diseases and orphan drugs, ensuring robust, reliable and high-quality evidence. Without patient-centred outcomes it was discussed that communications may not fully represent the patient.

"PCO data plays a significant role in drug approval processes, influencing key stakeholders throughout the drug lifecycle, such that collection of high quality and robust data can result in better decision making." (Article 19)

"…it's also important to get down to…the individual patient data level…so that people can see the variation within those small groups of patients." (Interview 3)

The development of PCOs or patient reported outcomes were discussed in the literature as being important in measuring clinical benefit and designing registries from a patient-centric perspective (Bellgard et al., 2017; Benjamin et al., 2017; Morel and Cano, 2017; Mulberg et al., 2019; Raffai and Timmis, 2017). PCOs were discussed as helping to make treatment decisions, improving orphan drug development, measuring

what matters to patients and communicating the clinical effectiveness of orphan drug therapy (Benjamin et al., 2017; Morel and Cano, 2017)

The clinical relevance of communications to patients was discussed, with clinical relevance having to be shown for communications to be successful.

"…the communication or not of the technology. So how relevant it is or isn't it to describe the technology to patients, you know all other stakeholders." (Interview 1)

"Clinical significance. This is key for us. If something is not based on a deep understanding of the interventions required to improve outcomes…it is a red flag with regard to the possible significance of the solution." (Article 8)

Whilst the importance of demonstrating clinical significance was not directly discussed in the literature, there was discussion around the importance of looking beyond clinical and economic outcomes, ensuring that outcomes are meaningful (Levinson, 2019).

Strategy, plan and launch

This superordinate theme discussed strategy, plan and launch as involving initiatives and being in tune with regulation, policy and following guidance to ensure effective communications. Collaborations and partnerships with all stakeholders were discussed as being important for an effective strategy, plan and launch.

Collaboration and partnerships. This subordinate theme revealed the importance of collaborations and partnerships between patient advocacy groups and all relevant stakeholders for developing impactful patient content, educating patients and improving healthcare practice. This was discussed as being important for effective communications.

"…collaboration between patient advocacy groups and the pharma industry to ensure that patients are educated around gene therapy and understand the benefits, but also the risks of having a gene therapy…" (Interview 2)

"…collaborative development of advice on improving better practice, where we work with experts to create impactful content that explains the unmet need…" (Article 10)

Collaborations were widely discussed in the literature, with the importance of international research consortia in improving therapy development for rare diseases, developing PCOs and interacting with patient organisations in a collaborative research network discussed (Blay et al., 2016; Julkowska et al., 2017; Lochmüller et al., 2017; Morel and Cano, 2017) Collaborations between patients and HCPs were discussed in their importance in putting information into context, working with rare disease patients using collaborative communications to fully participate in treatment decision making (Budych et al., 2012; Pogue et al., 2018).

Partnerships with advocacy groups were discussed in one of the interviews.

"Work in partnership with the advocacy groups so that you're developing the patient content with them and not isolating them..." (Interview 4).

The importance of partnerships was discussed in the literature, with the central role of patient advocacy groups in linking stakeholders together important for building collaborative partnerships and developing long-term communications (AMICULUM, 2014; Raffai and Timmis, 2017; Woodward et al., 2016). Partnerships were also discussed in the context of public-private partnerships with healthcare services and the rare disease community in developing treatments and patient registries (Groft, 2013; Hansen, 2012).

In the wider science communication literature collaborations between experts and laypersons are discussed as important in creating meaning and understanding according to the interactive model of communications (Gasiorek, 2018; Trench, 2008). Building collaborative teams are also discussed as important in developing content and implementing science communications (Cooke et al., 2017; Kuehne et al., 2014).

Regulation, policy, guidance and initiatives. This subordinate theme discussed the importance of having a clear understanding of regulation, policy and guidance. This was discussed as being vital to ensure communications are effective and abide by different regional and global regulations, policies and guidance. The importance of initiatives and their potential to help improve communications to meet the needs of patients was also discussed.

Guidelines and protocols were discussed in one of the interviews.

"…we have to have an industry that understands there are guidelines and protocols for engaging and communicating to patients." (Interview 2)

Whilst guidelines and protocols are not discussed in the direct context of engaging and communicating with patients, it has been suggested that healthcare communications professionals could used communication tools including the CDC clear communications index in developing content to

communicate with patients (Baur and Prue, 2014; Zhu et al., 2018). The importance of creating clear guidelines and protocols for using social media in interacting with patients has also been discussed in the literature, with policies and guidelines important to ensure its proper use and ensure content is of high quality and accurate (Milne and Ni, 2017; Sarasohn-Kahn, 2008).

A lack of standard healthcare guidelines due to the variation in rare diseases can present communication challenges (Ambrosini et al., 2018; Hannemann-Weber et al., 2011). The literature discussed the importance of clear protocols and guidelines for orphan drug economic evaluation models and the use of orphan drugs to ensure treatments reach patients (Pearson et al., 2018; Torrent-Farnell et al., 2018).

The early engagement with regulatory agencies was discussed in one of the articles.

"…an early understanding of the environment and engagement with regulatory and reimbursement agencies and payers." (Article 38)

There was discussion within the literature regarding the importance of engaging and communicating with health, political and regulatory agencies and authorities who make decisions about the use of orphan drugs (Blay et al., 2016; Giannuzzi et al., 2017; Goetghebeur et al.,

2017; Hansen, 2012; Mulberg et al., 2019; Pearson et al., 2018). Regulatory agencies were discussed as being important gatekeepers in the approval of drugs, stimulating effective orphan drug development and their use, with close collaborations with these agencies vital for communications (Hansen, 2012; Mulberg et al., 2019). Regulations were discussed in facilitating orphan drug development and definitions of what constitutes a rare disease and orphan product in Europe and the US (Darrow et al., 2018; Giannuzzi et al., 2017; Price, 2016). Regulations and regulatory compliance were discussed as important for safe and effective use of social media for communicating with rare disease patients and patients more generally (Milne and Ni, 2017; Sarasohn-Kahn, 2008).

The importance of policy for new interventions and treatments was discussed in one of the articles.

"…it's important to understand current clinical practice and policy levers that could create opportunities for your intervention." (Article 49)

Policies were mentioned in the literature, helping to ensure effective rare disease treatment and collaborations, with the importance of patient advocacy groups in communicating with policy makers discussed (Hansen, 2012; Torrent-Farnell et al., 2018). The importance of policies around the sharing of information on social media were also discussed (Milne and Ni, 2017; Pogue et al., 2018; Sarasohn-Kahn, 2008).

Initiatives were discussed in one of the articles in relation to standards when communicating health information.

"Initiatives such as the Information Standard, run by NHS England, give charities guidance and standards to adhere to when communicating health information, ensuring that it is evidence-based, clear and easy to understand." (Article 37)

Initiatives were discussed in the literature with regards to orphan drug development, definitions and incentives, with joint action initiatives in Europe discussed as important in raising awareness, allowing for close collaborations and improving the lives of those living with rare diseases (Giannuzzi et al., 2017; Lampert et al., 2016; Lynn et al., 2017; Price, 2016; Rinaldi, 2005).

Patients and stakeholders

This superordinate theme discussed the importance of stakeholders and patients who should be central to communications. This included the subordinate themes of co-creation, connectivity, education and networking, patient needs, rare disease therapy, and stakeholders and experts.

Co-creation. This subordinate theme discussed co-creating solutions and collaborating with patients, HCPs and other stakeholders. Communications were discussed as having to be planned through co-creation and collaboration, involving proactive and early engagement with all stakeholders. This was discussed as being particularly important for the evidence required for reimbursement and drug access.

"…lysosomal storage disorder conditions, Gaucher, Farber disease and the way that we developed that kind of communication plan there was to co-create with treatment centers within the NHS." (Interview 4)

"…HCP and patient steering committees can be very useful in co-creating the most effective support activities…This co-creation can extend into patient and caregiver support materials…" (Article 50)

Although co-creation in creating content and engaging with patients was not directly discussed in the literature, the internet was discussed as important in its potential to enable the co-creation of content with the rare disease community, with patient-centric communications relying on co-creation (Charles, 2014; Liuccio et al., 2015; Morgan et al., 2014; Tozzi et al., 2013; Walker, 2012; Zhu et al., 2018).

The importance of co-creation with experts and audiences has been discussed in the science communication literature for effective communications, drawing on principles from the engagement model of science communication (Cooke et al., 2017; Joubert, 2014; Trench, 2008; Wilsdon et al., 2004).

Connectivity. The importance of having connected communications to link all stakeholders across the whole treatment and healthcare pathway was discussed. The importance of having a connected patient community within a national and global network was discussed as being important for communications.

"…given the technology we have these days to connect healthcare professionals over wide geographies and ensure that the specialists in specific disease areas can collaborate..." (Interview 2)

"…increasing communities formed…as I think that as patients start to leverage their own capabilities to reach out to other patients and create a global network." (Interview 4)

Whilst there was no direct discussion of connectivity in global networks, the importance of global networks was discussed in relation to international research consortia and reference networks (AMICULUM, 2014; Blay et al., 2016; Julkowska et al., 2017; Lochmüller et al., 2017; Lynn et al., 2017; Woodward et al., 2016). Connectivity was discussed in relation to increasing the connectivity of patient registries and the importance of connectivity in online and virtual communities (Ambrosini et al., 2018; AMICULUM, 2014; Bellgard et al., 2017; Black and Baker, 2011; Dwyer et al., 2014; Liuccio et al., 2015; Milne and Ni, 2017; Paul et al., 2010; Richesson et al., 2009; Tamí-Maury et al., 2017; Tozzi et al., 2013; Woodward et al., 2016). Increased connectivity and the integration of regulatory agencies was discussed as being important to increase the effectiveness of orphan drug development (Giannuzzi et al., 2017).

Education and networking. Education and networking between patients and stakeholders was discussed as being important for communications, allowing for knowledge and information to be shared amongst stakeholders.

"…effective HCP networks would become critical to delivering this education and improving patient outcomes. These networks…would provide visibility for expert physicians and a platform to share and discuss experience." (Article 10)

"…more platforms that people could go on to learn more about the condition…" (Interview 5)

Networking and education was discussed in the literature, with the importance of continued HCP education in rare disease, orphan drugs, diagnosis and screening highlighted, with networking helping to address some of the unique needs in rare diseases (AMICULUM, 2014; Hansen, 2012; Lynn et al., 2017). It was highlighted by one publication that education and information provided should not be promotional in nature (AMICULUM, 2014). The importance of the internet and digital ways of providing education to HCPs and patients was discussed, especially the use of social networks in providing a platform for education and networking in rare disease and orphan drugs (Al-Jasmi et al., 2010; Black and Baker, 2011; Bouwman et al., 2010; Dwyer et al., 2014; Liuccio et al., 2015; Milne and Ni, 2017; Morgan et al., 2014; Walker, 2013; Zhu et al., 2018). Symposiums were also discussed as an important platform for networking and communications in rare cancers (Blay et al., 2016).

Patient needs

This subordinate theme discussed the unique needs of the patient that should shape communications, discussing topics involving patient engagement, groups, pathways and patient-centricity.

The importance of engaging with patient groups to ensure effective communications was discussed.

"Engage with a wide range of patient groups across relevant countries." (Article 18)

Patient advocacy groups were discussed as helping to empower the patient and provide them with a collective voice. Communications with these groups from relevant stakeholders was also discussed as having to be patient friendly, ensuring patients are well informed so they can make better more informed healthcare decisions.

"…patient advocacy groups are often experts in their disease…it is therefore critical to build on patient representation to ensure that their voice resonates through all communication." (Article 10)

"If you look at the spark website, you know their explanation of gene therapy is really…patient friendly." (Interview 2)

The importance of understanding the whole patient pathway for effective communications was discussed. This was discussed as being important for patient diagnosis, accessing treatments and support services.

"If you fail to understand the patient pathway and how your drug fits into it, you may struggle to convert access into commercial success." (Article 26)

"…not just look at that small part of the pathway…but look broader and look to support the whole pathway…" (Interview 2)

Patient-centricity was discussed as being vital for effective communications by capturing the patient perspective and taking a patient-centric approach to communications.

"…trying to capture the patient perspective in communications is also very very important…" (Interview 3)

"Creating a truly patient-centric approach must become pharma's mantra." (Article 36)

There was a large amount of discussion in the literature around patient needs covering the topics discussed in this subordinate theme, each topic essential to ensure communications meet the needs of the patient

(Ambrosini et al., 2018; AMICULUM, 2014; Bellgard et al., 2017; Benjamin et al., 2017; Black and Baker, 2011; Blay et al., 2016; Charles, 2014; Hannemann-Weber et al., 2011; Levinson, 2019; Liuccio et al., 2015; Lochmüller et al., 2017; Milne and Ni, 2017; Morel and Cano, 2017; Pearson et al., 2018; Pinto et al., 2016; Raffai and Timmis, 2017; Sarasohn-Kahn, 2008; Schieppati et al., 2008; Tozzi et al., 2013; Walker, 2013; Woodward et al., 2016; Zhu et al., 2018).

Stakeholders and experts. This subordinate theme highlighted that there are many stakeholders, experts, key players and specialists that need to be considered when communicating. It was discussed that all relevant groups should be involved and includes, but is not limited to, advisory boards, biotechnology companies, key opinion leaders, medical affairs professionals and liaisons, medical writers, payers, steering committees and umbrella organisations.

For example the importance of key opinion leaders (KOLs) in communicating was highlighted.

"…it is in developing and communicating the science behind these strategies where KOLs can be appropriately engaged." (Article 51)

Within the literature there was a focus on KOLs and HCPs who are important stakeholders when it comes to communications in rare disease

and orphan drugs (AMICULUM, 2014; Budych et al., 2012; Hannemann-Weber et al., 2011; Hansen, 2012; Huyard, 2009; Tozzi et al., 2013; Urwin et al., 2016).

Future directions

This superordinate theme discussed some important future directions, possible solutions to improve communications and the factors that may be important for communications in the near future. This was revealed in interviews and articles, including the subordinate themes of collaboration, data and evidence, and framework and system.

Collaboration. This subordinate theme discussed how collaborations and education around gene therapies, its risks, benefits and long-term efficacy would be central to future communications, exemplified below.

"…requirements for good collaboration between patient advocacy groups and the pharma industry to ensure that patients are educated around gene therapy and understand the benefits, but also the risks of having a gene therapy and the potential durability of it." (Interview 2)

Collaborations and their importance to communications have been discussed elsewhere in the superordinate themes of message, content and delivery, and strategy, plan and launch.

Data and evidence. This subordinate theme discussed the importance of having clear data and evidence gathering for future communications. This was discussed as needing to occur across the whole patient pathway, with constant high quality data needed to ensure the value proposition and efficacy of an orphan drug can be monitored and analysed effectively.

The importance of data and evidence in future communications was discussed in the interviews. This was discussed in terms of ensuring there is a clear understanding of the data needed for the reimbursement of orphan drugs in the long and short-term.

"…a clearer reimbursement strategy…greater coming together of what you're going to have to demonstrate and to whom…there will be clarity…people will be understanding what they need to gather to provide that data…." (Interview 1)

This data and evidence will be crucial and need to be communicated via the correct channels to all stakeholders and those who make payment decisions as discussed in the interview below.

"…making sure that those data sets are generated first of all, then analysed and then sent out through various communications…that will be crucial…" (Interview 3)

The importance of data and evidence has been discussed elsewhere in the superordinate themes of challenges, and information, data and evidence.

Framework and system. This subordinate theme discussed that innovative healthcare systems, treatment pathways and structures are required around orphan drugs to improve communications in the future. This was discussed as requiring a systematic approach to communications, with a basic understanding and framework around rare disease communications and a change in mind-set of the relevant stakeholders. This was revealed in interviews, exemplified below. Some of these topics have been discussed elsewhere in the results and discussion section.

A more systematic approach to communications was suggested to ensure communications are effective and meet the needs of different audiences as discussed below.

"...systematic approach in making sure that the communications that you're getting out are informative about and also cover off on those different needs of the different audiences..." (Interview 3)

This has been discussed in the literature in the context of understanding the patient pathway and healthcare ecosystem. This has been discussed elsewhere in the subordinate themes including healthcare ecosystem, patients, and patient needs.

The development of a clear framework of communications around orphan drugs was also discussed as important in improving communications to relevant stakeholders.

"…we'll know what the framework is…That then would be communicated by whoever is relevant to that particular stakeholder." (Interview 1)

The development of a communications framework was not discussed in the literature.

A change in mind-set was also discussed as needing to change and evolve with patients and health systems to improve communications.

"…mind-set needs to change. And as such there communications with patients and with the health systems also needs to evolve." (Interview 2)

It was also discussed that treatment pathways for patients and the reimbursement of orphan drugs will change as a result of more drugs coming to market, with an impact for healthcare communications.

"…It's anticipated that 40 to 60 gene therapies will come to market in the next five years…I think that is going to have a huge impact on healthcare professional communications…" (Interview 2)

Conclusion

This thematic analysis and critical review highlighted the different aspects of communications in rare diseases and the post-commercial launch of orphan drugs. This enabled the assessment of the current landscape and potential future directions of communications in this area. A number of different superordinate and subordinate themes were discussed revealing that communications are complex and do not occur in isolation, dependent on a number of factors including *information, data and evidence, strategy, plan and launch, and patients and stakeholders.* Key communication aspects where highlighted with communications associated with a number of challenges, some highlighted by this analysis with potential future directions discussed.

Communications around rare diseases and orphan drugs involves the whole patient pathway and not just the post-commercial stage as revealed by this thematic analysis (AMICULUM, 2014; Bellgard et al., 2017; Blay et al., 2016; Darrow et al., 2018; Goetghebeur et al., 2017; Jiménez et al., 2018; Julkowska et al., 2017; Levinson, 2019; Liuccio et al., 2015; Morel and Cano, 2017; Pearson et al., 2018; Raffai and Timmis, 2017).

Whilst this critical review aimed to focus on the post-commercial phase of orphan drug communications, it became apparent that communications cannot be taken in isolation and must include an understanding of the

whole rare disease patient pathway from diagnosis, management and treatment for effective communications with this population, with patients central to communications (Ambrosini et al., 2018; AMICULUM, 2014; Bouwman et al., 2010; Charles, 2014; Groft, 2013; Hansen, 2012; Jiménez et al., 2018; Levinson, 2019; Liuccio et al., 2015; Melnikova, 2012; Morel and Cano, 2017; Raffai and Timmis, 2017; Walker, 2012).

Findings were in line with communication theory, discussing the importance of bi-directional models of communication, with communications being an open dialogue with all stakeholders (AMICULUM, 2014, 2014; Budych et al., 2012; Charles, 2014; Cooke et al., 2017; Gasiorek, 2018; Joubert, 2014; Lee and Garvin, 2003; Levinson, 2019; Trench, 2008; Windover et al., 2014; Woodward et al., 2016). For effective communications in rare diseases and orphan drugs a clear understanding of both science and healthcare communication strategies and theories are required (Blumler and Katz, 1974; Cooke et al., 2017; Glanz and Bishop, 2010; Kuehne et al., 2014; Lee and Garvin, 2003; Levinson, 2019; Trench, 2008; Windover et al., 2014).

Fully utilising communication models and theories including the shared decision-making model and the uses and gratification theory could help to improve communications in rare disease and orphan drugs, enabling the effective co-creation of patient-centric content (Budych et al., 2012; Charles, 2014; Hannemann-Weber et al., 2011; Ruggiero, 2000; So,

2012; Vogel et al., 2009; Walker, 2012; Zhu et al., 2018). This would be in line with dialogue communication models and ensure communications are bi-directional and collaborative (Abma and Broerse, 2010b; AMICULUM, 2014; Cooke et al., 2017; Joubert, 2014; Lee and Garvin, 2003; Levinson, 2019; Trench, 2008; Woodward et al., 2016).

One of the ways in which communications around rare diseases and orphan drugs could be improved is through the creation of an orphan drug specific registry, hub or database. This could provide centralised information about orphan drugs that could be easily accessed and communicated with the relevant stakeholders. Rare disease patient registries and registry development have been discussed in this thematic analysis in their importance in collecting data on rare diseases (Ambrosini et al., 2018; Bellgard et al., 2017; Cavero-Carbonell et al., 2016; Groft, 2013; Julkowska et al., 2017; Lochmüller et al., 2017; Mulberg et al., 2019; Paul et al., 2010; Richesson et al., 2009; Torrent-Farnell et al., 2018; Woodward et al., 2016). These rare disease registries could incorporate information about orphan drugs for specific rare disease conditions once they come to market. This could be in a lay summary format to effectively inform and communicate with HCPs and patients about orphan drugs.

Limitations

This study was limited as it only focused on Open Health as a case study and can only give an idea of communications, challenges and future directions in relation to the current landscape and future directions of communications about the post-commercial launch of orphan drugs. Whilst coding of themes was informed by peer-reviewed articles, identification of themes was subjective, an issue associated with thematic analysis (Braun and Clarke, 2006; Nowell et al., 2017; Starks and Trinidad, 2007; Vaismoradi et al., 2016). Due to the flexibility of analysis there is potential for inconsistency when developing themes, as there is no predefined coding process, which can reduce the dependability of findings (Nowell et al., 2017; Vaismoradi et al., 2016).

Summary

By conducting this critical analysis using thematic analysis methodology, insight into communications around rare disease and orphan drugs was provided. This will help to stimulate discussion on communications and how this can be improved in relation to the post-commercial launch of orphan drugs to treat rare diseases.

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Bibliography

Abma, T.A., Broerse, J.E.W., 2010a. Patient participation as dialogue: setting research agendas: Patient participation as dialogue. Health Expectations 13, 160–173.

Abma, T.A., Broerse, J.E.W., 2010b. Patient participation as dialogue: setting research agendas: Patient participation as dialogue. Health Expectations 13, 160–173.

Al-Jasmi, F., Moldovan, L., Clarke, J.T., 2010. Hunter disease eClinic:interactive, computer-assisted, problem-based approach to independent learning about a rare genetic disease. BMC Med Educ 10, 72.

Alliance for Regenerative Medicine, 2019. Getting Ready: Recommendations for Timely Access to Advanced Therapy Medicinal products (ATMPs) in Europe.

Ambrosini, A., Calabrese, D., Avato, F., Catania, F., Cavaletti, G., Pera, M., Toscano, A., Vita, G., Monaco, L., Pareyson, D., 2018. The Italian neuromuscular registry: a coordinated platform where patient organizations and clinicians collaborate for data collection and multiple usage. Orphanet Journal of Rare Diseases 13.

AMICULUM, 2014. Communication strategies for rare diseases: uncommon opportunities.

Anderson, M., Elliott, E.J., Zurynski, Y.A., 2013. Australian families living with rare disease: experiences of diagnosis, health services use and needs for psychosocial support. Orphanet J Rare Dis 8, 22.

Bassett, B.R., 2012. Encyclopedia of Case Study Research: Iterative. SAGE Publications, Inc., 2455 Teller Road, Thousand Oaks California 91320 United States.

Baur, C., Prue, C., 2014. The CDC Clear Communication Index Is a New Evidence-Based Tool to Prepare and Review Health Information. Health Promotion Practice 15, 629–637.

Bellgard, M.I., Napier, K.R., Bittles, A.H., Szer, J., Fletcher, S., Zeps, N., Hunter, A.A., Goldblatt, J., 2017. Design of a framework for the deployment of collaborative independent rare disease-centric registries: Gaucher disease registry model. Blood Cells, Molecules and Diseases 68.

Benjamin, K., Vernon, M.K., Patrick, D.L., Perfetto, E., Nestler-Parr, S., Burke, L., 2017. Patient-Reported Outcome and Observer-Reported Outcome Assessment in Rare Disease Clinical Trials: An ISPOR COA Emerging Good Practices Task Force Report. Value in Health 20, 838–855.

Berger, J., 2014. Word of mouth and interpersonal communication: A review and directions for future research. Journal of Consumer Psychology 24, 586–607.

Black, A.P., Baker, M., 2011. The impact of parent advocacy groups, the Internet, and social networking on rare diseases: The IDEA League and IDEA League United Kingdom example: The Impact of Parent Advocacy Groups. Epilepsia 52, 102–104.

Blay, J.-Y., Coindre, J.-M., DucimetièRe, F., Ray-Coquard, I., 2016. The value of research collaborations and consortia in rare cancers. The Lancet Oncology 17, e62–e69.

Blumler, J.G., Katz, E. (Eds.), 1974. The Uses of mass communications: current perspectives on gratifications research, Sage annual reviews of communication research. Sage Publications, Beverly Hills.

Boice, N., Kishnani, Dr.P.S., Philipson, T., Levin, D., Kent, A., Hendriksz, Dr.C., Drummond, M., 2013. Rare disease Impact Report: insights from patients and the medical community. Shire.

Bouwman, M.G., Teunissen, Q.G.A., Wijburg, F.A., Linthorst, G.E., 2010. "Doctor Google" ending the diagnostic odyssey in lysosomal storage disorders: parents using internet search engines as an efficient diagnostic strategy in rare diseases. Archives of Disease in Childhood 95, 642–644.

Braddy, P.W., Meade, A.W., Kroustalis, C.M., 2008. Online recruiting: The effects of organizational familiarity, website usability, and website attractiveness on viewers' impressions of organizations. Computers in Human Behavior 24, 2992–3001.

Braun, V., Clarke, V., 2006. Using thematic analysis in psychology. Qualitative Research in Psychology 3, 77–101.

Braun, V., Clarke, V., Hayfield, N., Terry, G., 2018. Thematic Analysis. In: Liamputtong, P. (Ed.), Handbook of Research Methods in Health Social Sciences. Springer Singapore, Singapore, pp. 1–18.

Bruine de Bruin, W., Wong-Parodi, G., 2014. The role of initial affective impressions in responses to educational communications: The case

of carbon capture and sequestration (CCS). Journal of Experimental Psychology: Applied 20, 126–135.
Budych, K., Helms, T.M., Schultz, C., 2012. How do patients with rare diseases experience the medical encounter? Exploring role behavior and its impact on patient–physician interaction. Health Policy 105, 154–164.

Burke-Garcia, A., Scally, G., 2014. Trending now: future directions in digital media for the public health sector. Journal of Public Health 36, 527–534.

Cavero-Carbonell, C., Gras-Colomer, E., Guaita-Calatrava, R., López-Briones, C., Amorós, R., Abaitua, I., Posada, M., Zurriaga, O., 2016. Consensus on the criteria needed for creating a rare-disease patient registry. A Delphi study. Journal of Public Health 38, e178–e186.

Charles, S., 2014. Patient-Centricity is Essential For Rare Disease Communications [WWW Document]. INSTINCTIF.com. URL https://instinctif.com/insights/patient-centricity-is-essential-for-rare-disease-communications/ (accessed 7.18.19).

Cooke, S.J., Gallagher, A.J., Sopinka, N.M., Nguyen, V.M., Skubel, R.A., Hammerschlag, N., Boon, S., Young, N., Danylchuk, A.J., 2017. Considerations for effective science communication. FACETS 2, 233–248.

Darrow, J.J., Avorn, J., Kesselheim, A.S., 2018. The FDA Breakthrough-Drug Designation — Four Years of Experience. The New England Journal of Medicine 378, 1444–1453.

Dudo, A., 2015. Scientists, the Media, and the Public Communication of Science: Scientists' Public Communication Activities. Sociology Compass 9, 761–775.

Dutta-Bergman, M.J., 2004. Primary Sources of Health Information: Comparisons in the Domain of Health Attitudes, Health Cognitions, and Health Behaviors. Health Communication 16, 273–288.

Dwyer, A.A., Quinton, R., Morin, D., Pitteloud, N., 2014. Identifying the unmet health needs of patients with congenital hypogonadotropic hypogonadism using a web-based needs assessment: implications for online interventions and peer-to-peer support. Orphanet J Rare Dis 9, 83.

European Commission, 2014. Implementation report on the Commission Communication on Rare Diseases: Europe's challenges [COM(2008) 679 final] and Council Recommendation of 8 June 2009 on an action

in the field of rare diseases (2009/C 151/02) (Implementation report). European Commission, Brussels.

European Medical Agency, 2015. Orphan medicinal product designation.

European Medical Agency, 2019a. Orphan medicines in the EU - Leaving no patient behind.

European Medical Agency, 2019b. Marketing authorisation [WWW Document]. European Medical Agency. URL https://www.ema.europa.eu/en/glossary/marketing-authorisation (accessed 7.18.19).

European Medical Agency, 2019c. Post-authorisation safety stuides (PASS) [WWW Document]. URL https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/post-authorisation-safety-studies-pass-0 (accessed 7.18.19).

Evaluate, 2019. Orphan Drug Report 2019 (No. 6).

Evans, W.R., 2018. Dare to think rare: diagnostic delay and rare diseases. Br J Gen Pract 68, 224.3-225.

Fox, N.J., 2008. The SAGE Encyclopedia of Qualitative Research Methods. SAGE Publications, Inc., 2455 Teller Road, Thousand Oaks California 91320 United States.

Gasiorek, J., 2018. Chapter 5: Traditional models of human communication. In: Message Processing: The Science of Human Communication. University of Hawai'i OER.

Genetic and Rare Diseases Information Center, 2017. FAQS About Rare Diseases [WWW Document]. rarediseases.info.nih.gov. URL https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases (accessed 6.25.19).

Giannuzzi, V., Conte, R., Landi, A., Ottomano, S., Bonifazi, D., Baiardi, P., Ceci, A., 2017. Orphan medicinal products in Europe and United States to cover needs of patients with rare diseases: an increased common effort is to be foreseen. Orphanet Journal of Rare Diseases 12.

Glanz, K., Bishop, D.B., 2010. The Role of Behavioral Science Theory in Development and Implementation of Public Health Interventions. Annu. Rev. Public Health 31, 399–418.

Goetghebeur, M., Wagner, M., Samaha, D., O'Neil, W., Badgley, D., Castro-Jaramillo, H., Abrishami, P., Sarria-Santamera, A., Cleemput,

I., Tringali, M., 2017. EXPLORING VALUES OF HEALTH TECHNOLOGY ASSESSMENT AGENCIES USING REFLECTIVE MULTICRITERIA AND RARE DISEASE CASE. International Journal of Technology Assessment in Health Care 33, 504–520.

Groft, S.C., 2013. Rare Diseases Research - Expanding Collaborative Translational Research Opportunities. Chest 144, 16–23.

Hallberg, L.R.-M., 2006. The "core category" of grounded theory: Making constant comparisons. International Journal of Qualitative Studies on Health and Well-being 1, 141–148.

Hannemann-Weber, H., Kessel, M., Budych, K., Schultz, C., 2011. Shared communication processes within healthcare teams for rare diseases and their influence on healthcare professionals' innovative behavior and patient satisfaction. Implementation Science 6.

Hansen, J.-C., 2012. Rare Diseases and Orphan Drugs: A comprehensive approach of strategic perspectives. Journal of Communication in Healthcare 5, 199–219.

Huyard, C., 2009. What, if anything, is specific about having a rare disorder? Patients' judgements on being ill and being rare: Patients' judgements on being ill and being rare. Health Expectations 12, 361–370.

Jiménez, A., Ais, A., Beaudet, A., Gil, A., 2018. Determining the value contribution of selexipag for the treatment of pulmonary arterial hypertension (PAH) in Spain using reflective multi-criteria decision analysis (MCDA). Orphanet Journal of Rare Diseases 13.

Joppi, R., Gerardi, C., Bertele', V., Garattini, S., 2016. Letting post-marketing bridge the evidence gap: the case of orphan drugs. BMJ i2978.

Joubert, M., 2014. Handbook series: Essay 5: Science communication - an introduction to theory and trends. Stellenbosch University.

Julkowska, D., Austin, C., Cutillo, C., Gancberg, D., Hager, C., Halftermeyer, J., Jonker, A., Lau, L.P., Norstedt, I., Rath, A., Schuster, R., Simelyte, E., Van Weely, S., 2017. The importance of international collaboration for rare diseases research: a European perspective. Gene Therapy 24, 562–571.

King, A., Hoppe, R.B., 2013. "Best Practice" for Patient-Centered Communication: A Narrative Review. Journal of Graduate Medical Education 5, 385–393.

Korstjens, I., Moser, A., 2018. Series: Practical guidance to qualitative research. Part 4: Trustworthiness and publishing. European Journal of General Practice 24, 120–124.

Kotecha, R.S., Kees, U.R., Cole, C.H., Gottardo, N.G., 2015. Rare childhood cancers-an increasing entity requiring the need for global consensus and collaboration. Cancer Med 4, 819–824.

Kuehne, L.M., Twardochleb, L.A., Fritschie, K.J., Mims, M.C., Lawrence, D.J., Gibson, P.P., Stewart-Koster, B., Olden, J.D., 2014. Practical Science Communication Strategies for Graduate Students: Graduate Student Science Communication. Conservation Biology 28, 1225–1235.

Lampert, A., Hoffmann, G., Ries, M., 2016. Thirty Years of Orphan Drug Legislation and the Development of Drugs to Treat Rare Seizure Conditions: A Cross Sectional Analysis. PLoS One 11, e0161660.

Lee, R.G., Garvin, T., 2003. Moving from information transfer to information exchange in health and health care. Social Science & Medicine 56, 449–464.

Levinson, N., 2019. Pathway to Launch Excellence: OPEN Health Consulting outlines a Triple-A framework for a successful drug launch.

Limb, L., Nutt, S., Sen, A., 2010. Experiences of Rare Diseases: An Insight from Patients and Families.

Lincoln, Y.S., Guba, E.G., 1985. Naturalistic inquiry. Sage Publications, Beverly Hills, Calif.

Liuccio, M., Belotti, R., Comune, A., Zambito, V., Schulz, P., 2015. Communication in Rare Diseases: a Literature Review. Journal of Communications Research 7, 10.

Lochmüller, H., Jonker, A., Baynam, G., Kaufmann, P., Dawkins, H., Lasko, P., Austin, C., Boycott, K., 2017. The International Rare Diseases Research Consortium: Policies and Guidelines to maximize impact. European Journal of Human Genetics : EJHG 25, 1293–1302.

Lynn, S., Hedley, V., Atalaia, A., Evangelista, T., Bushby, K., 2017. How the EUCERD Joint Action supported initiatives on Rare Diseases. European Journal of Medical Genetics 60, 185–189.

Marshall, M.N., 1996. Sampling for qualitative research. Fam Pract 13, 522–526.

McClellan, J., King, M.-C., 2010. Genetic Heterogeneity in Human Disease. Cell 141, 210–217.

Melnikova, I., 2012. Rare diseases and orphan drugs. Nature Reviews Drug Discovery 11, 267–268.

Milne, C.-P., Ni, W., 2017. The Use of Social Media in Orphan Drug Development. Clinical Therapeutics 39, 2173–2180.

Morel, T., Cano, S., 2017. Measuring what matters to rare disease patients - reflections on the work by the IRDiRC taskforce on patient-centered outcome measures. Orphanet Journal of Rare Diseases 12.

Morgan, T., Schmidt, J., Haakonsen, C., Lewis, J., Della Rocca, M., Morrison, S., Biesecker, B., Kaphingst, K.A., 2014. Using the Internet to Seek Information About Genetic and Rare Diseases: A Case Study Comparing Data From 2006 and 2011. JMIR Res Protoc 3, e10.

Mulberg, A., Bucci-Rechtweg, C., Giuliano, J., Jacoby, D., Johnson, F., Liu, Q., Marsden, D., Mcgoohan, S., Nelson, R., Patel, N., Romero, K., Sinha, V., Sitaraman, S., Spaltro, J., Kessler, V., 2019. Regulatory strategies for rare diseases under current global regulatory statutes: a discussion with stakeholders. Orphanet J. Rare Dis. 14.

National Academies of Sciences, Engineering, and Medicine (U.S.) (Ed.), 2017. Communicating science effectively: a research agenda. The National Academies Press, Washington, DC.

Nowell, L.S., Norris, J.M., White, D.E., Moules, N.J., 2017. Thematic Analysis: Striving to Meet the Trustworthiness Criteria. International Journal of Qualitative Methods 16, 160940691773384.

Open Health, 2019. News and Views [WWW Document]. openhealthgroup.com. URL https://www.openhealthgroup.com/news (accessed 8.9.19).

Paul, L., Claude, M., Ana, R., Loïc, L.M., Eric, D., Mohamed, B.S., Jean-Philippe, J., Laurent, T., Geneviève, B., Eva, B.-L., Marion, G.-B., Christine, B., Rémi, S., Ségolène, A., Martine, L.M., Alain, V., 2010. CEMARA an information system for rare diseases. Studies in Health Technology and Informatics 481–485.

Pearson, I., Rothwell, B., Olaye, A., Knight, C., 2018. Economic Modeling Considerations for Rare Diseases. Value in Health 21, 515–524.

Pillai, R., Jayasree, K., 2017. Rare cancers: Challenges & issues. Indian J Med Res 145, 17.

Pinto, D., Martin, D., Chenhall, R., 2016. The involvement of patient organisations in rare disease research: a mixed methods study in Australia. Orphanet J Rare Dis 11, 2.

Pogue, R.E., Cavalcanti, D.P., Shanker, S., Andrade, R.V., Aguiar, L.R., de Carvalho, J.L., Costa, F.F., 2018. Rare genetic diseases: update on diagnosis, treatment and online resources. Drug Discovery Today 23, 187–195.

Polich, G.R., 2012. Rare disease patient groups as clinical researchers. Drug Discovery Today 17, 167–172.

Price, J., 2016. What Can Big Data Offer the Pharmacovigilance of Orphan Drugs? Clinical Therapeutics 38, 2533–2545.

Raffai, F., Timmis, O., 2017. Building the patient community. Gene Therapy 24, 547–550.

Rare Disease UK, 2018. What is a rare disease? [WWW Document]. raredisease.org.uk. URL https://www.raredisease.org.uk/what-is-a-rare-disease/ (accessed 6.25.19).

Richesson, R.L., Lee, H.S., Cuthbertson, D., Lloyd, J., Young, K., Krischer, J.P., 2009. An automated communication system in a contact registry for persons with rare diseases: Scalable tools for identifying and recruiting clinical research participants. Contemporary Clinical Trials 30, 55–62.

Richter, T., Nestler-Parr, S., Babela, R., Khan, Z.M., Tesoro, T., Molsen, E., Hughes, D.A., 2015. Rare Disease Terminology and Definitions—A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group. Value in Health 18, 906–914.

Rinaldi, A., 2005. Adopting an orphan. EMBO Rep 6, 507–510.

Ruggiero, T.E., 2000. Uses and Gratifications Theory in the 21st Century. Mass Communication and Society 3, 3–37.

Sarasohn-Kahn, J., 2008. The Wisdom of patients: Health Care Meets Online Social Media. California HealtHCare foundation.

Schieppati, A., Henter, J.-I., Daina, E., Aperia, A., 2008. Why rare diseases are an important medical and social issue. The Lancet 371, 2039–2041.

Schumacher, K.R., Stringer, K.A., Donohue, J.E., Yu, S., Shaver, A., Caruthers, R.L., Zikmund-Fisher, B.J., Fifer, C., Goldberg, C., Russell, M.W., 2014. Social Media Methods for Studying Rare Diseases. PEDIATRICS 133, e1345–e1353.

Sharon, A.J., Baram-Tsabari, A., 2014. Measuring mumbo jumbo: A preliminary quantification of the use of jargon in science communication. Public Underst Sci 23, 528–546.

Simpson, A., 2016. The hidden costs of rare diseases: A feasibility study.

So, J., 2012. Uses, Gratifications, and Beyond: Toward a Model of Motivated Media Exposure and Its Effects on Risk Perception. Communication Theory 22, 116–137.

Starks, H., Trinidad, S.B., 2007. Choose Your Method: A Comparison of Phenomenology, Discourse Analysis, and Grounded Theory. Qual Health Res 17, 1372–1380.

Stones, S.R., Smith, J., 2018. Social media supremacy: a force of change paving the way for the next generation of healthcare and research. Evid Based Nurs 21, 2–3.

Tamí-Maury, I., Brown, L., Lapham, H., Chang, S., 2017. Community-based participatory research through virtual communities. Journal of Communication in Healthcare 1–7.

Torrent-Farnell, J., Comellas, M., Poveda, J.L., Abaitua, I., Gutiérrez-Solana, L.G., Pérez-López, J., Cruz, J., Urcelay, J., Lizán, L., 2018. The view of experts on initiatives to be undertaken to promote equity in the access to orphan drugs and specialised care for rare diseases in Spain: A Delphi consensus. Health policy 122, 590–598.

Torres, D.H., Pruim, D.E., 2019. Scientific storytelling: A narrative strategy for scientific communicators. Communication Teacher 33, 107–111.

Tozzi, A.E., Mingarelli, R., Agricola, E., Gonfiantini, M., Pandolfi, E., Carloni, E., Gesualdo, F., Dallapiccola, B., 2013. The internet user profile of Italian families of patients with rare diseases: a web survey. Orphanet J Rare Dis 8, 76.

Trench, B., 2008. Towards an Analytical Framework of Science Communication Models. In: Cheng, D., Claessens, M., Gascoigne, T., Metcalfe, J., Schiele, B., Shi, S. (Eds.), Communicating Science in Social Contexts. Springer Netherlands, Dordrecht, pp. 119–135.

Tuckett, A.G., 2005. Applying thematic analysis theory to practice: A researcher's experience. Contemporary Nurse 19, 75–87.

Tustin, N., 2010. The Role of Patient Satisfaction in Online Health Information Seeking. Journal of Health Communication 15, 3–17.

Urwin, D., Fookes, M., Petrie, D., van Der Laan, S., Dawkins, H., 2016. Survey of healthcare experiences of Australian adults living with rare diseases. Orphanet Journal of Rare Diseases 11.

U.S Food and Drugs Administration, 2018. Post-Approval Stuides [WWW Document]. U.S Food and Drugs Administration. URL https://www.fda.gov/medical-devices/postmarket-requirements-devices/post-approval-studies (accessed 7.18.19).

Vaismoradi, M., Jones, J., Turunen, H., Snelgrove, S., 2016. Theme development in qualitative content analysis and thematic analysis. JNEP 6, p100.

Valdez, R., Ouyang, L., Bolen, J., 2016. Public Health and Rare Diseases: Oxymoron No More. Prev. Chronic Dis. 13, 150491.

Vogel, B.A., Leonhart, R., Helmes, A.W., 2009. Communication matters: The impact of communication and participation in decision making on breast cancer patients' depression and quality of life. Patient Education and Counseling 77, 391–397.

Walker, K.K., 2012. Thoracic outlet syndrome on the top consumer health/medical websites: A case for continuing healthy people 2020 quality of health-related website objectives. Journal of Communication in Healthcare 5, 75–83.

Walker, K.K., 2013. Rare disease-specific social media sites: An opportunity for collaboration. Journal of Communication in Healthcare 6, 71–76.

Wellman-Labadie, O., Zhou, Y., 2010. The US Orphan Drug Act: Rare disease research stimulator or commercial opportunity? Health Policy 95, 216–228.

Wilsdon, J., Willis, R., Demos (Organization : London, E., 2004. See-through science: why public engagement needs to move upstream. Demos, London.

Windover, A.K., Boissy, A., Rice, T.W., Gilligan, T., Velez, V.J., Merlino, J., 2014. The REDE Model of Healthcare Communication: Optimizing Relationship as a Therapeutic Agent. Journal of Patient Experience 1, 8–13.

Woodward, L., Johnson, S., Beck, J., Gasteyger, C., Licht, C., Ariceta, G., 2016. An innovative and collaborative partnership between patients with rare disease and industry-supported registries: the Global aHUS Registry. Orphanet Journal of Rare Diseases 11.

Zhu, X., Smith, R.A., Parrott, R.L., Worthington, A.K., 2018. Understanding information sharing about rare diseases: an evaluation of the NIH's website on AATD. Journal of Communication in Healthcare 11, 128–139.