Exploring Patient Engagement in Pharmaceutical Medicine Development: A Value Creation Perspective

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A thesis submitted to the University of Gloucestershire in accordance with the requirements of the degree of PhD in the School of Health & Social Care

Submission: November 2020

Acknowledgement

I like to thank people that have accompanied me through this academic journey.

First, I am deeply grateful to my two supervisors – Dr Joy Darch and Dr Lily Wang - for guiding me through this challenging research process. Their ability to pose inspiring questions and demand deeper thinking, paired with compassion and constant encouragement, was pivotal for me to continually improve the thesis and complete this piece of work. Their support is the backbone of this dissertation.

Next, I like to thank the interview participants of this study who helped me to dig deeply into the research topic and generate insights by learning from their valuable perspectives and experiences.

Finally, I am grateful to my family for their understanding and support when on many evenings and weekends over the past five years I was immersed in working on my thesis and away from them. Particularly, I hope my research journey inspires my two boys - Benjamin and Paul – to chase their own passion by overcoming obstacles and setbacks with resilience and perseverance.

Abstract

Patient engagement (PE) has rapidly expanded in medicine development in recent years. Despite the volume of literature on this concept, there has been little conceptualization of this new phenomenon, which is still ambiguous and fragmented. A clear understanding of PE in medicine development from a value-creation perspective is much advocated, yet sparsely studied in the literature.

Taking a social constructivist stance, this study found PE in medicine development as a multi-dimensional and multi-level complex social phenomenon. Therefore, a holistic account of PE in medicine development from the perspectives of key stakeholders (i.e., patient, society, and PHARMA) was developed to answer the *what* and *how* questions regarding PE in medicine development from a value-creation perspective.

This study explored the concept of PE in medicine development through identifying the antecedents, attributes, consequences and influencing factors of PE in medicine development, employing Rodgers' (1989) concept development approach. Thereby, a thematic analysis of interviews with key stakeholders (i.e., patients, medicine developers, and PE experts) and literature provided the following PE definition in medicine development:

> *Patient engagement in medicine development means co-creation of value for patients, healthcare and all healthcare stakeholders through partnership and collaboration between healthcare actors and patients along the medicine development lifecycle, to allow integration of patient value in medicine development by engaging the patients as value co-creators of health outcomes*.

This study revealed that PE in medicine development requires alignment among healthcare stakeholders on value perspectives based on *patient value*. Thereby, *co-creation* was found as a core attribute, while *patient centricity* a core antecedent and *improved value*

a core consequence of PE in medicine development. The PE conceptual framework and theoretical propositions developed in this study offer a conceptualization of PE in medicine development, providing foundational work and practical guidance to healthcare actors to further advance this concept in theory and practice.

Declaration

I declare that the work in this thesis was carried out in accordance with the regulations of the University of Gloucestershire and is original, except where indicated by specific references in the text. No part of the thesis has been submitted as part of any other academic award. The thesis has not been presented to any other educational institution in the United Kingdom or overseas.

Any views expressed in the thesis are those of the author and in no way represent those of the University.

Signed

Date: 24th November 2020

doi: 10.46289/ME66RS16

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List of abbreviations

ASN	American Society of Nephrology
AHA	American Heart Association
BIO	Biotechnology Innovation Organisation
BRA	Benefits and Risks Assessment
CASP	Critical Appraisal Skills Programme
CIHR	Canadian Institutes of Health Research
CIOMS	Council for International Organisations of Medical Science
CEI	Cutting Edge Information
COA	Clinical Outcome Assessment
CTTI	Clinical Trials Transformation Initiative
DIA	Drug Information Association
EBM	Evidence-Based Medicine
EFPIA	European Federation of Pharmaceutical Industries and Associations
ESL	Ethical, Social, Legal
EMA	European Medicines Agency
EMBASE	Excerpta Medica dataBASE
EPF	European Patients Forum
EU	European Union
EUPATI	European Patients' Academy
FDA	Food and Drug Administration
FPM	Faculty of Pharmaceutical Medicine
GDL	Goods-Dominant Logic
GDPR	General Data Protection Regulation
HA	Health Authority
HCP	Healthcare Professional
HrQoL	Health-related Quality of Life
IAPO	International Alliance of Patients' Organisations
IFAPP	International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine
IMI	Innovative Medicine Initiative
IOM	Institute of Medicine
KPI	Key Performance Indicator

MA	Marketing Authorisation
MD	Medicine Developer
N	Number
NASEM	National Academies of Sciences, Engineering, and Medicine Forum on Drug Discovery, Development, and Translation
NCRI	National Cancer Research Institute
NEJM	New England Journal of Medicine
NICE	National Institute for Health and Clinical Excellence
NIH	National Institute of Health
NHC	National Health Council
PE	Patient Engagement
PIS	Participant Information Sheet
PX	Patient Engagement Expert
PT	Patient
P-xx	Participant identifier
PCDD	Patient-centred Drug Development
PCORI	Patient-centred Outcome Research Institute
PFDD	Patient-focussed Drug Development
PFMD	Patient-focussed Medicines Development
PGE	Patient Group Engagement
PHARMA	Pharmaceutical Company
PhRMA	Pharmaceutical Research and Manufacturers of America
P5	Predictive, personalised, preventive, participatory, psycho-cognitive
PPI	Patient and public involvement
PO	Patient Organisation
PR	Public Relation
PRO	Patient-reported Outcomes
PROM	Patient-reported Outcomes Measures
R&D	Research & Development
ROI	Return on Investment
RO	Research Objective
RQ	Research Question
SDL	Service-Dominant Logic
TA	Thematic analysis

TPP	Target Product Profile
UIC	University of Illinois AT Chicago
UOG	University of Gloucestershire
VBM	Value-Based Medicine
VCC	Value Co-Creation
ViE	Value-in-Exchange
ViU	Value-in-Use
WHO	World Health Organisation
WOS	Web of sciences

Glossary of key terms

Concepts/Terms	Description
Business Value	…refers to the expected positive consequences associated with PE in medicine development for a PHARMA company in terms of better innovation, improved reputation, and financial benefits.
Co-construction	…describes the gradual engagement and connecting process of patients and professionals in setting up a relationship based on the complementarity of one another's expertise and experiential knowledge in order to carry out a joint activity from a common understanding to create mutual value.
Co-creation	…a general concept rooted in service science that emphasizes the joint creation of value by companies and customers through interaction, with customers having an active role in the co-design and co-production of offerings and, lastly, the co-construction of value as purpose through the usage of offerings.
Co-design	…a specific construct of value co-creation with a user-centric focus where people collaboratively developing and creating things conceptually to address challenges and develop solutions – a step prior to co-production.
Co-production	…with its scholarly origin in the public sector and industrial economy, co-production refers to collaboration between professional services providers and customers with a focus on implementation and delivering of service offerings.
Healthcare Value	… means the positive results in collective patient outcomes, safety, and satisfaction at an affordable cost, in association with a medicinal product and/or treatment.
Integration of patient value	…refers to a means of interaction with patients to incorporate patient inputs, experience and needs into the medicine development life cycle.
Partnership & collaboration	…refers to the interaction between patients and HCPs through shared leadership and joint decision-making based on principles of reciprocity, respect, trust, co-learning, equality, and transparency.
Patient Activation	…is related to the cognitive and behavioural components of patients' attitudes toward healthcare and is conceptualised as an incremental attitude that the patient may develop through interaction with HCPs.
Patient as consumer and expert	…refers to the ethical argument that patients are consumers of healthcare with the right to take part in PE in medicine development that affects their life. Patients have unique experiential knowledge as experts whose input should be captured through PE in medicine development.
Patient as value co-creator	…refers to the belief that patients' experiential knowledge is an asset and a resource; they should be involved in medicine development life cycle as co-creators to optimise healthcare outcomes.
Patient centricity	…refers to a company strategy that puts the needs of patients and carers at the centre of a company's thinking and actions, equal to the need for profit, permeating and informing all aspects of the business.
Patient Compliance/ Adherence	…focuses on the behavioural components of the patients' care experience, referring to the extent to which the patient's behaviour matches the clinician's recommendations through interaction with HCPs.

Patient Consultation	…patients are involved in a reactive role in providing information or feedback without being involved in decision-making through interaction with HCPs.
Patient Empowerment	…describes the patients' subjective sense of control over their disease and treatment management and the feeling of being responsible for their health outcomes through interaction with HCPs.
Patient Involvement	… redefines patients from being passive recipients of information to actively choosing to take part in healthcare activities that have an impact on their health.
Patient Participation	…implies the patient is in an active role. Refers to a relational patient-doctor exchange that allows shared treatment decision-making through interaction with HCPs.
Patient Partnership	…recognises that patients have assets, such as experiential knowledge and ability, which can be brought to add value in medicines and healthcare through interaction with HCPs.
Patient Value	…means the unique preferences, concerns, and expectations of individual patients towards medical treatment; and positive results in patient's outcome, safety, and satisfaction at a reasonable and affordable cost
Value	…from SDL perspective, value is determined by the beneficiary based on the "value-in-use" that results from the beneficial application of the resources among actors through collaboration.
Value-Based Medicine	…means the practice of medicine incorporating the highest level of evidence-based data with the patient-perceived value conferred by health care interventions for the resources spent.
Value Co-Creation	…describes occurrences in which companies and customers generate value jointly through interactions.
Value-in-Exchange	…concerns the resources, knowledge, and market offerings in the provider's sphere, used as a value foundation to facilitate customer's fulfilment of value.
Value-in-Use	…concerns the customer's fulfilment of value through experience, personalisation, and relationship.
Scientific Evidence	…means clinical efficacy, effectiveness, safety, benefits, and risks data of a medicine gathered from biomedical sciences and clinical practices.
Service-Dominant Logic	…postulates value is fundamentally derived and determined in use – the integration and application of resources in a specific context – rather than in exchange – embedded in firm output and captured by price.

1 Introduction

1.1 Background

Operating in a healthcare environment, medicine development is a science-driven and highly regulated discipline where, conventionally, patients are treated as research subjects rather than customers (Brown & Brown, 2013). 'Patients' in this context refers to 'individuals who have personal experience of a particular disease, condition, or treatment, along with caregivers of those individuals and representatives of relevant patient organisations' (von Tigerstrom, 2016, p. 28). In recent years, the concept of patient engagement (PE) has rapidly expanded in the healthcare sector, drawing on the notion that medical treatment aims to improve the patient's health, and value should be created and measured around the beneficiaries – the patients (Porter, 2010). PE marks the evolution of healthcare from a disease-centred to a patient-centred paradigm (Brown & Bussell, 2011). This paradigm shift in the healthcare environment has had a significant impact on medicine development practices in the pharmaceutical industry (PHARMA), whose business aims are to deliver innovative medicines to improve patients' health and healthcare outcomes in society (Bae, 2015).

Over the past decade, regulatory authorities including the European Medicines Agency (EMA), Food and Drug Administration (FDA), National Institute for Health and Clinical Excellence (NICE) and National Institute of Health (NIH) have increasingly recognised and endorsed the need for PE in the context of medicine development from a public health perspective in these regions. Several guidance documents on PE in the healthcare sector – where the pharmaceutical industry is a key healthcare product and service provider – have been released, with the aim of enhancing PE implementation in the context of medicine development and capturing PE benefits (EMA, 2016a, 2017; FDA, 2009, 2018b; NICE, 2015; NIH, 2011). Furthermore, a significant number of PE initiatives have been

launched by multiple healthcare stakeholders in response to new guidance regarding PE in medicine development: (i) PE programmes initiated by academic healthcare associations (ASN, 2017; CIHR, 2014; IOM, 2001, 2012; NASEM, 2018; NEJM, 2016, 2017); (ii) PE programmes initiated by patient organisations (EPF, 2013; EUPATI, 2016a, 2016b, 2016c, 2016d, 2016e; NHC, 2015a, 2015b, 2016); (iii) PE programmes initiated by regulators (DIA, 2016, 2017; PFMD, 2018a, 2018b); and (iv) PE programmes initiated by pharmaceutical associations (BIO, 2017; CTTI, 2018; CUTTINGEDGE, 2016; EFPIA, 2007, 2011; IFPMA, 2012; IMI, 2018). The USA was considered the front-runner in the advancement of PE in medicine development, triggered by the patient-focused drug development (PFDD) initiative introduced by FDA (2018b), followed by the EU and UK (EMA 2017; NICE, 2015). These broad initiatives have demonstrated the significance accorded to the phenomenon of PE by all relevant healthcare stakeholders, which resonates with the acknowledgement that healthcare is moving towards a more patient-centred paradigm and that PE is thus a strategic imperative (Dentzer, 2013). The potential role of PE in healthcare improvement has been described as 'the blockbuster drug of the century' (Kish, 2012, p. 1), indicating the high social expectations of PE, which is becoming the heart of healthcare and medicine (Dentzer, 2013).

Despite the widely acknowledged potential of this new concept, the acceptance and establishment of PE in the context of medicine development are still perceived as very challenging (Accenture, 2014; Armstrong & Bloom, 2017; Eyeforpharma, 2015, 2017a, 2017b; PatientView, 2016) and the following issues have been widely discussed in the literature: (i) the lack of a common understanding about the *what* and *how* questions regarding PE (du Plessis et al., 2017; Perfetto & Oehrlein, 2015; Lowe et al., 2016; Mitchell, Bance, Feldman & Reznik, 2017; Perfetto, Oehrlein, Boutin, Reid & Gascho, 2017; Pushparajah, 2018; Yeoman et al., 2016); (ii) different priorities and conflicts of interest

among healthcare stakeholders (Blasimme & Vayena, 2016; Carman & Workman, 2017); (iii) differing views on the patients' role in the context of medicine development (Crawford, Matczak, Moore, Haydar & Coderre, 2017; Hahn et al., 2017; Marzorati & Pravettoni, 2017); (iv) the lack of a methodological framework combining the science-driven biomedical research with the patient-centred, value-driven PE approach (Kelly, Heath, Howick & Greenhalgh, 2015; Messina & Grainger, 2012; Sacristan et al., 2016); and (v) the lack of evidence to substantiate the feasibility and value of PE in the context of medicine development (Bloom et al., 2018; Croft & McLoughlin, 2015; H. Wilson et al., 2018).

Taking these issues into account, it is evident that there is little theoretical clarity around the concept of PE in the context of medicine development, in particular from a value-creation perspective, which merits further investigation to reach a common understanding about what PE means and how value can be created through PE in medicine development (Lowe et al., 2016). These identified knowledge gaps motivated me to develop a theoretical core and definition of the concept of PE in the context of medicine development, necessary starting points for further concept development in terms of measurement, generating evidence and offering practical guidance for effective PE implementation (Beecher, Devane, White, Greene & Dowling, 2017; Duncan, Cloutier & Bailey, 2007; Imenda, 2014; Liehr & Smith, 1999; Risjord, 2009).

1.2 Research objectives and questions

The research questions (RQs) for the present study are:

(1) What does the concept of PE in medicine development mean?

(2) How are PE in medicine development understood and perceived by key healthcare stakeholders?

(3) How can PE in medicine development be conceptualized from a value-creation perspective?

Thereby, the research objectives (ROs) of the present study are to:

(1) explore current understandings of the concept of PE in the context of medicine development from a value-creation perspective.

(2) explore practices and perceptions regarding the concept of PE in the context of medicine development from the perspectives of key stakeholders from a value-creation perspective.

(3) develop a PE conceptual framework and theoretical propositions in the context of medicine development from a value-creation perspective, informed by the above understandings.

The research objectives of the present study are addressed by (i) reviewing the concept of PE in the context of healthcare and medicine development in the extant literature to capture current understandings and knowledge gaps; (ii) exploring the attributes, antecedents, consequences, barriers, facilitators, surrogate terms, related concepts, empirical examples of PE in medicine development through a thematic analysis of the data in the literature; (iii) exploring practical understanding and experiences regarding the concept of PE in the context of medicine development from the perspectives of key stakeholders in order to generate empirical data through interviews; (iv) interrogating and triangulating data collected from both the thematic analysis of the literature and the interviews to identify core themes around the concept of PE in the context of medicine development; and (v) developing a PE conceptual framework and theoretical propositions in the context of medicine development from a value-creation perspective, based on the above understandings.

1.3 Originality of the research

My interest in embarking on this research originated while I was working in the research and development (R&D) department of a large pharmaceutical company

(PHARMA), developing innovative medicines through addressing the unmet medical needs of patients was a key task of my job. As the topic of PE was increasingly debated in the context of pharmaceutical medicine development, I started to ask myself what PE in medicine development means, how I could apply PE in my medicine development practices and what benefits could be achieved by including PE in medicine development. Initially, I had many more questions than answers and even more doubts about the value and feasibility of PE, in common with most of my colleagues in the field of medicine development.

From a professional standpoint, I am familiar with conventional medicine development processes from my work as a medicine development director in a pharmaceutical company. The starting point of any medicine development programme is defining the target product profile (TPP) of a potential medicine by considering the efficacy and safety potentials of the medicine in the context of the treatment landscape of a specific disease or condition. The pharmacological characterisation of the molecule of interest and the epidemiological research into understanding the disease are the major inputs in defining the TPP of a potential medicine. There has been rarely direct interaction with patients (as the consumers and beneficiaries of the medicines to be developed) to elicit their perspectives at this early stage of medicine development. When a potential medicine is in the late stages of clinical development, large patient populations are recruited as study subjects to test its effects, in order to derive a population-based statistical determination of the efficacy and safety profile of the potential medicine and prepare for the label claim approval, which is the basis for the commercial success of a medicinal product. The patient voice has rarely been heard in the development of conventional medicine, which is considered the domain of scientists, physicians, and regulators rather than lay people such as patients. Information on disease conditions and treatment effects is gathered predominantly through interaction with the prescribing physicians, as a proxy for the patients, because they are healthcare

professionals (HCP) with the necessary medical knowledge to discuss the scientific issues concerning medicine development with PHARMA, speaking the same language (Domecq et al., 2014; Kelly et al., 2015; Crawford et al., 2017; Duffett, 2017).

Several years ago, the concept of PE was introduced into the context of medicine development by health authorities (HAs), emphasising the presence of the patient voice in medicine development processes, in a move considered to be triggered by increased patient power in the healthcare environment (Carman et al., 2013; Hoos et al., 2015; Lowe et al., 2016). Following this guidance from the HAs about PE in medicine development, it became necessary to capture patients' input in the medicine development process and to treat patients as customers and experts about their conditions (du Plessis et al., 2017; Kirwan et al., 2017; Mitchell et al., 2017). However, despite the high societal attention given to the concept of PE in medicine development, I experienced a lack of understanding and scepticism of this new phenomenon within the pharmaceutical medicine development environment. At this point, I became curious about PE and started to read journal articles on this subject. After reading Perfetto et al.'s (2017) scholarly article '*Value to whom? The patient value in the value discussion*', and Kelly et al.'s (2015) discussion of '*The importance of values in evidence-based medicine*', I was inspired to explore the concept of PE in medicine development from a value-creation perspective, which I believed could help us understand this new phenomenon and address the elements missing in practice. Moreover, the 'what' and 'how' questions about PE in the context of medicine development have been suggested as a critical research problem calling for further study by several scholars (Bloom et al., 2018; Boudes et al., 2018; Duffett, 2017), which further motivated me to search for answers to these questions about PE in medicine development through the present thesis.

More than six decades ago, Merck (1950) famously spoke of the value of medicine for patients, and the link between the value for the patient and the profit for PHARMA:

> ‘We try to remember that medicine is for the patient. We try never to forget that medicine is for the people. It is not for the profits. The profits follow, and if we have remembered that they have never failed to appear. The better we have remembered it, the larger they have been.’ (p. 1)

This widely cited speech from an eminent figure in PHARMA veteran reveals that PHARMA, as commercial enterprises, always aim to generate commercial profit to survive competition, although the strategic focus and the means used to achieve this aim may differ. ‘Patient value’ is clearly claimed by Merck (1950) as the primary focus, which then achieves the profit goals. Put differently, if patient value is the primary goal, the company profits for PHARMA should follow. In putting patient value first, PHARMA is encouraged to adopt patient engagement (PE) and patient centricity as strategic imperatives for business success (Croft & McLoughlin, 2015; CUTTINGEDGE, 2016). Following Merck’s (1950) principle, PE is not a new idea within PHARMA, so why does the concept of PE in medicine development still gain so much attention in the twenty-first century?

Drawing on the literature, patient centricity and patient engagement in healthcare settings share the belief that patients are customers of healthcare services and, therefore, should be put at the core of all healthcare activities (Burns, Bellows, Eigenseher & Gallivan, 2014; du Plessis et al., 2017). These principles concur with the concepts of ‘customer centricity’ and ‘customer engagement’, which have long been established in other industries (Devasirvatham, 2012; Galvagno & Dalli, 2014; Gambetti & Graffigna, 2014) and are built on the theories of value co-creation (VCC) and service-dominant logic (SDL), which have been widely used in marketing and management disciplines across many industries for decades (Prahalad & Ramaswamy, 2004; Vargo, Maglio & Akaka, 2008). VCC describes

the notion that companies and customers generate value together through interactions, based on the core SDL principle that value is always determined by the customer as the beneficiary and, therefore, the customer is always a co-creator of value (Prahalad & Ramaswamy, 2004; Vargo et al., 2008). Despite the underlying theoretical link of the VCC and SDL theories with the concept of PE, these theoretical perspectives have, to date, rarely been discussed in relation to PE in the context of medicine development because, conventionally, the therapeutic value of a medicine in terms of efficacy and safety is considered the primary goal in medicine development, rather than creating patient value, defined as the preferences, concerns and expectations of an individual patient regarding the medical treatment (Sackett, Straus, Richardson, Rosenberg & Haynes, 2000). Furthermore, the prescribing physicians, rather than the patients were considered the primary customers of PHARMA in the past, (Etgar, 2008; Fang, Palmatier & Evans, 2008) and direct interaction with patients in the context of medicine development was even deliberately avoided by PHARMA due to perceived legal and regulatory constraints (Etgar, 2008; Fang, Palmatier & Evans, 2008; Gurtner & Soyez, 2016). In the past decade, with increased patient empowerment in healthcare and medicine decision-making, patients have gained greater attention as consumers of healthcare services and the medicines developed by PHARMA (Armstrong, Mullins, Gronseth & Gagliardi, 2017; Brett et al., 2010; von Tigerstrom, 2016). The changing role of patients, or the empowering of patients, in healthcare has triggered the introduction of value-based medicine (VBM), which draws on patient value and patient centricity as key concepts and is thus in tune with the core theoretical values of VCC and SDL in other industries (G. C. Brown, Brown & Sharma, 2003; Porter, 2010). The paradigm shift to VBM, with patient value at the heart of healthcare, forces PHARMA to re-focus on patients and interact with them as the primary customers and value co-creators in the context of medicine development (Marzorati & Pravettoni, 2015). PE is thus becoming increasingly

relevant for PHARMA in their medicine development strategies and operations, tasked with developing medicines to serve patients and healthcare bodies (du Plessis et al., 2017; Eyeforpharma, 2015).

Critical literature reviews on the concept of PE in the context of medicine development revealed the following gaps in the current knowledge base: (i) little conceptualization and theoretical development of the concept of PE in medicine development (i.e., what does PE in medicine development mean? How PE can be conceptualized in the context of medicine development?) (Boutin et al., 2017; Carman et al., 2013; Domecq et al., 2014); (ii) a lack of a consistent methodological framework for a value-driven PE approach in medicine development (i.e. what are the core themes concerning PE in medicine development from a value-creation perspective?) (Frank et al., 2015; Higgins, Larson & Schnall, 2017; Hoos et al., 2015); and (iii) a lack of understanding of how value can be created by PE in medicine development to guide effective PE implementation in practices (i.e. what kind of value for whom, with what kind of mechanism?) (Lowe et al., 2016). These knowledge gaps are discussed in detail in the following paragraphs, drawing on findings from earlier studies, based on which the research questions and research objectives of the present study are derived and justified.

In the context of healthcare, Carman et al. (2013) proposed a multi-dimensional framework for PE within healthcare, covering patient, organisation and society levels, which helps structure understandings of PE and illustrate the factors influencing the occurrence of PE in practice. However, the article lacked a theoretical perspective to support the further conceptualization of PE in medicine development. Higgins et al. (2017) conducted a concept analysis of PE in the health disciplines, based on a systematic literature review using Rodgers' (1989) evolutionary approach. In this study, the defining attributes of PE in the context of health were identified as personalisation, access, commitment, and therapeutic alliance. The

article concluded that the concept of PE in the context of health involved both process and behaviour and was shaped by the relationship between the patient and the healthcare delivery system (Higgins et al., 2017). Despite the insights derived from thorough scrutiny of the literature, this study was limited by a lack of empirical data to support the findings. Another systematic review conducted by Domecq et al. (2014) combined a literature review with expert consultation using a meta-narrative approach, which focused on how best to conduct PE in healthcare research, considering the feasibility of such activities in practice. This study suggested that little conceptualization and theoretical development was available on the concept of PE in this field but was urgently needed to guide PE practices (Domecq et al., 2014). Additionally, drawing on principles of health economics in the field of patient-centred outcome research (PCOR), Frank et al. (2015) offered a PE conceptual model organised around the elements of foundations, actions and outcomes in the specific context of PCOR. The key principles found within this PE conceptual model were trust, honesty, co-learning, transparency, reciprocal relationship, partnership, and respect (Frank et al., 2015). The model was based on practical experiences of PCOR initiatives, which offers a basis for evaluating the quality of PE activities for PCOR initiatives. However, the study was limited by its narrow scope within the PCOR context, and also by a lack of conceptual exploration for research beyond the PCOR initiatives despite the practical focus on patient involvement from the PCOR organisational perspective. The findings from the above studies indicate that, despite wider discussion and eager piloting of the concept of PE within several specific healthcare settings (i.e., healthcare services, health, PCOR), its theoretical core remains vague and ambiguous, impeding the knowledge development and effective application of PE in practice. Consequently, research is needed to establish the meaning of the concept of PE in the context of use as a baseline starting point to advance our knowledge of it (Domecq et al., 2014). (see ***Table 1***).

In the context of medicine development, four major pieces of literature were found which contribute to current understandings of PE from different stakeholder perspectives. A PE framework across medicine research and development, regulatory review and market access was proposed by Hoos et al. (2015) with a focus on improving clinical trial design and conduct, based on the model developed by the National Health Council (NHC, 2008). Hoos et al. (2015) hypothesised that establishing routine PE in medicine development will lead to more relevant, impactful, and better patient outcomes, but the article lacked theoretical explanation and empirical evidence to support this claim. Further, the authors argued that a systematic master PE framework in the context of medicine development, endorsed by all healthcare stakeholders, was the crucial next step in the effective adoption of PE throughout the medicine development life cycle (Hoos et al., 2015). Another conceptual framework for PE throughout the medicine development life-cycle was elaborated by Perfetto and Oehrlein (2015), who illustrated what a meaningful PE could look like in the clinical development, health authority approval, post-approval and communication phases. The framework was developed within the patient-focused drug development (PFDD) initiatives, with input from regulators, patient representatives and pharmaceutical practitioners to employ science-based methods to gather valid and representative data reflecting patients' perspectives (Perfetto & Oehrlein, 2015). Despite the practical guidance offered for meaningful PE in the context of medicine development, an obvious limitation of this article is the absence of a theoretical foundation for the proposed framework. An empirical study by Lowe et al. (2016), based on semi-structured interviews with participants from pharmaceutical companies and patient organisations, identified the primary areas where PE could contribute value in the context of medicine development: product strategy, clinical trials, patient-reported outcome (PRO) development and evidence generation. The study concluded that more evidence was necessary to support the

hypothesised positive effect of PE in medicine development, and that this was not possible without a consistent PE methodology framework serving as a foundation for measurement (Lowe et al., 2016). However, this study offered no clear definition of PE in the context of medicine development and the related theoretical cores (see ***Table 1***).

Table 1: literature findings and knowledge gaps concerning PE in the context of healthcare and medicine

Literature	Study type	Findings	Context	Knowledge Gaps
Carman et al., 2013	Scholarly article	PE model in healthcare was discussed covering: • Organisational design & governance • Policymaking	Healthcare policy	• Changes in policy and healthcare organisations are needed to embrace PE. • Little conceptual development
Domecq et al., 2014	Systematic review	Focus on how to conduct PE in: • Patient selection methods • Engagement methods • Exploration of barriers and challenges	Healthcare Research	• Little conceptualisation and theoretical development. • Future research needed to identify best methods to implement PE.
Frank et al., 2015	Theoretical research	PE model for patient-centred outcome research covering: • Foundational elements • Actions • Outcomes	Health-economics	• Focuses on outcome research. • The link between PE elements and beneficial effects demands further research.
Hoos et al., 2015	Scholarly article	A systematic PE framework was suggested for: • Industry-led medicine research • Regulatory decision-making • Market access	Medicine development	• A meta systematic framework involving all healthcare stakeholders is considered necessary. • Theoretical underpinnings are divergent and unclear.
Perfetto et al., 2015	Scholarly article	A patient-focussed drug development (PFDD) model was constructed: • Patients and stakeholders need to be engaged through the whole life cycle of medicine	Medicine development	• The science of PE is still emerging, especially for medicine development. • PE methods are to be developed and tested against benefits.
Lowe et al., 2016	Empirical study	Opportunities for PE in medicine development identified as: • Product strategy • Clinical trials • Patient-Reported Outcome (PRO) development • Real-life evidence generation	Medicine Development	• Pharma needs to demonstrate product value relative to the patient experience. • A consistent methodology framework for PE in medicine development is needed.
Higgins et al., 2017	Systematic review	PE concept attributes: • Personalisation • Access • Commitment • Therapeutic alliance	Healthcare Services	• Literature research only, no empirical data available. • Specific role of PE concept in various contexts is to be determined and measured.
Boutin et al., 2017	Scholarly article	Priority areas to facilitate the implementation of PE are: • Culture and process change • Development of a global meta-framework for PE	Medicine development	• Practical focus initiated by patient organisations. • Theoretical underpinning unexplored

Most recently, drawing on the concept of patient as partner and the widespread agreement that PE has become a priority for many healthcare stakeholders, key themes relating to PE in the context of medicine development were elucidated by Boutin et al. (2017) in a scholarly article covering culture and process change, development of a PE meta-

framework for training and information exchange. This article drew similar conclusions to those above about the current sporadic and inconsistent approach to PE, the need for a common understanding of meaningful PE and for a means to measure PE value to enable effective implementation in medicine development (Boutin et al., 2017). Drawing on the knowledge gaps identified from the systematic approach to a literature review discussed above (summarized in ***Table 1***), the research aims of the present study were developed: to conceptualize the PE phenomenon in the context of medicine development from a value-creation perspective and to offer greater theoretical clarity regarding this concept. The adoption of a value-creation theoretical perspective for the conceptualization of PE in medicine development in the present study is further discussed and justified in Section 2.5.

Given the lack of knowledge about PE in the context of medicine development, the present study will contribute to a better understanding of the concept of PE in medicine development from a value-creation perspective (i.e., what does PE in medicine development mean? How can PE in medicine development be conceptualized from a value-creation perspective?). It places particular focus on exploring the understandings and perceptions of PE in the context of medicine development from the perspectives of relevant stakeholders (i.e., patients, medicine developers, and PE experts - people having professional knowledge and practical experiences in the field of PE in medicine development), in order to understand the significance and relevance of this concept in theory and practice. This study will contribute to the body of knowledge in both management and medicine development disciplines by offering theoretical clarity on the concept of PE in medicine development in terms of presenting core themes regarding this concept. Furthermore, a PE conceptual framework developed with input from key stakeholders in the present study will establish consensus understandings and develop meaningful guidance for practitioners. The identified research problems and knowledge gaps regarding PE in medicine development, as evidenced

by the existing literature, are linked with the research objectives (ROs) of the present thesis (see ***Table 2***) to illustrate the original contribution of this study.

***Table 2**: Research problems, knowledge gaps, contribution of the present thesis*

Research problems (see section 1.1)	**Critical knowledge gaps** (see section 1.3)	**Contribution of the present thesis** (see section 1.2)
The lack of a common understanding about *what* and *how* questions regarding PE in medicine development	Little conceptualization and theoretical development of the concept of PE in medicine development (i.e., what does PE in medicine development mean? How PE can be conceptualized in the context of medicine development?)	RO1: explore current understandings of the concept of PE in the context of medicine development from a value-creation perspective
Different priorities and conflicts of interest among healthcare stakeholders		RO2: explore practices and perceptions regarding the concept of PE in the context of medicine development from the perspectives of key stakeholders from a value-creation perspective
Differing views on the patients' role in the context of medicine development		
The lack of a methodological framework combining the science-driven biomedical research with the patient-centred, value-driven PE approach in medicine development	A lack of a consistent conceptual framework for a value-driven PE approach in medicine development (i.e., what are the core themes concerning PE in the context of medicine development from a value-creation perspective?)	RO3: develop a PE conceptual framework and theoretical propositions in the context of medicine development from a value-creation perspective, informed by the above understandings
The lack of evidence to substantiate the feasibility and value of PE in the context of medicine development	A lack of understanding of how value can be created by PE in medicine development to guide effective PE implementation. (i.e., what kind of value for whom, with what kind of resources and mechanism ?)	

1.4 Logic and outline of thesis

To address the research objectives and research questions most effectively, this thesis is structured as follows:

Chapter 1 provides background information on the topic of PE in the context of healthcare and medicine development and elucidates the research problems to be addressed and why it is important to understand the PE phenomenon in the context of healthcare and medicine development. The research objectives and questions, researcher's motivations, and activities to be undertaken to address the research objectives are elaborated upon. Lastly, the originality and contribution of the present study to the current knowledge base are discussed and justified based on the evidence of the literature.

Chapter 2 offers a systematic critical review of the current literature to identify what is already known about the concept of PE in the context of healthcare and medicine development; how the key terms and related concepts have been defined and changed over time and which theoretical perspectives related to the concept of PE are discussed in the existing body of knowledge. The literature concerning value-based medicine (VBM), value co-creation (VCC) and service-dominant logic (SDL) in the context of healthcare and medicine development is also explained and its relevance to the concept of PE in medicine development discussed. In this regard, the literature findings on PE conceptualizations are analysed to justify the adoption of an initial theoretical perspective for this thesis based on the VBM, VCC and SDL theories. This initial theoretical perspective serves as a lens to explore PE in the context of medicine development from a value-creation perspective to address the research questions in the present study, which then informs the selection of the most appropriate research methodology and design for the present study.

Chapter 3 describes the research methodology and study design used to address the research questions. The researcher's epistemological and ontological stance concerning the research questions is presented and justified. The research methodology framework based on Rodgers' (1989) evolutionary concept development approach is discussed and justified in relation to the research objectives and the research paradigm. This chapter also describes the data collection and analysis methods used in the theoretical, fieldwork, and final analytical phases of the present study, and the recruitment strategy and sampling methods for the semi-structured interviews during the fieldwork phase. The issue of trustworthiness in a qualitative study such as this is discussed and, finally, consideration is given to the ethical issues and measures taken in the present study to ensure compliance.

Chapters 4 presents the analysis and findings from the theoretical phase based on an inductive and qualitative thematic analysis of literature samples employed as a data source,

following the methodological framework of Rodgers' (1989) conceptual development approach (as described and justified in chapter 3). This chapter explores PE in medicine development through identifying the antecedents, attributes, consequences, facilitators, barriers, surrogate terms, related concepts, and empirical examples of PE in medicine development according to Rodgers (1989). The thematic analysis of the literature as data in this chapter is separate and goes beyond the literature review provided in chapter 2. A provisional thematic map of PE in medicine development is developed inductively and presented in this theoretical phase, which addresses the first research objective of the present study.

Chapter 5 presents the analysis and findings from the fieldwork phase. A second thematic map of PE in medicine development is developed and presented based on interviews, where the practices and perceptions of PE in medicine development from the perspectives of key stakeholders are captured and analysed through thematic analysis. This addresses the second research objective of the present study.

Chapter 6 presents the results from the final integrated analysis, through the triangulation of findings from both theoretical and fieldwork phases. A final definition of PE in medicine development is developed, based on the key defining attributes of PE found in the present study. The emerging core themes and patterns identified in the final analysis are presented and further conceptualized from a value-creation perspective, leading to the development of a PE conceptual framework with theoretical propositions in medicine development. This addresses the third research objective of the present study.

Chapter 7 presents the final discussion and conclusions. It discusses the findings and the new insights derived from the present study in the context of the existing knowledge, with regards to originality, similarity, differences, and implications. This chapter reflects on the research questions of the present study in relation to the findings and articulates the

theoretical contributions and practical recommendations offered in this study. The credibility, reliability, quality, strengths, and limitations of the present research are considered and, finally, areas for future research in this field are proposed for the further advancement of knowledge. The logic and outline of the thesis are presented in ***Figure 1***.

***Figure 1**: Logic and outline of thesis*

2 Literature review

2.1 Introduction

The previous chapter discussed the foundation of this study and explained the background, rationale, aims and research questions in relation to the identified research issues. It also set out how the present study could contribute to knowledge in the field of patient engagement (PE) in the context of medicine development.

This chapter critically reviews the current literature on the concept of PE in the context of healthcare (including all the activities and efforts made to promote, restore or maintain health with the involvement of multiple stakeholders through a healthcare system) (WHO, 2006) and pharmaceutical medicine development (including processes of research and development, regulatory review and approval, health technology assessment and market access) (Dubois et al., 2016). The purposes of this chapter are to (i) situate the present study within the current body of knowledge; (ii) justify the theoretical perspective based on value-creation to explore the PE phenomenon; and (iii) justify the originality and contributions of the present study to expand extant knowledge.

A review of the literature on current understandings of PE in the context of healthcare is relevant as it presents the broader context framing pharmaceutical medicine development activities. Furthermore, it provides a societal perspective of PE in pharmaceutical medicine development (Boutin et al., 2017; Carman et al., 2013; Lowe et al., 2016). The critical literature reviews on the concept of PE in the context of healthcare are therefore presented in Section 2.3 to set out the broad context framing the medicine development. Thereafter, a more focused literature reviews of PE in the context of medicine development are presented and discussed in Section 2.4, to identify the key aspects and knowledge gaps of PE in medicine development discussed in the literature, to justify the adoption of an initial theoretical perspective based on value-based medicine (VBM), value co-creation (VCC),

and service-dominant logic (SDL), which are considered appropriate to serve the research objectives of this study (see in-depth discussion in Section 2.5).

The available definitions of PE in the context of healthcare and medicine development are examined in this chapter and the related terms and concepts pertaining to the PE discussed in these contexts. This chapter also discusses the relevant theoretical perspectives of VBM, VCC and SDL in relation to the concept of PE in medicine development. These theoretical perspectives were suggested to be the key theoretical foundations underlying the concept of PE in medicine development as substantiated by the literature (du Plessis et al., 2017; Hoos et al., 2015; Lowe et al., 2016; Yeoman et al., 2016), which were considered vital to the understanding of the PE phenomenon in the context of medicine development. Therefore, in-depth discussions concerning the key aspects of these theoretical perspectives are offered in Section 2.5.1 and Section 2.5.2 respectively. As a result, theoretical perspectives based on VBM, VCC and SDL are adopted as a lens through which to explore the concept of PE in medicine development in the present study, which is discussed in Section 2.5.3. Furthermore, the links between these theoretical perspectives, the concept of PE in medicine development, and the research questions of the present study are elucidated and justified in this chapter.

2.2 Definition of key terms

PE is associated with the notion that 'patient value' is an integral part of medicine development in delivering valuable health outcomes for patients (Perfetto et al., 2017; Sackett et al., 2000). The notion of patient value has progressively shifted the focus of healthcare and medicine development from conventional evidence-based medicine (EBM) to value-based medicine (VBM*)* in the past decade (Bae, 2015; K. Fulford, 2004). Patient value is defined as the unique preferences, concerns and expectations of patients concerning medical treatment and is the key concept within the VBM theory (Sackett et al., 2000). VBM

was first introduced by Brown et al. (2003, p. 1) as 'the practice of medicine incorporating the highest level of evidence-based data with the patient-perceived value conferred by healthcare interventions for the resources expended'. Building on the notion of patient value, Porter (2010) defined healthcare value as health outcomes achieved per dollar spent around the patient. In essence, Porter's (2010) definition of healthcare value and Brown et al.'s (2003) VBM theory seek to incorporate patient value (measured as health outcomes from the patient's perspective) into science-dominated, evidence-based healthcare and medicine development, thus shifting healthcare and medicine development to an increasingly patient-centric paradigm with priority given to patient value (Bae, 2015). As they operate in a healthcare environment, a more patient-centric medicine development approach is therefore considered necessary for the pharmaceutical companies (PHARMA) to ensure their alignment with this paradigm shift to VBM, in order to serve the needs of patients and society (Boutin et al., 2017; Hoos et al., 2015; Kelly et al., 2015; Lowe et al., 2016).

Moreover, the concept of PE involves the notion that the patient becomes an active participant at the centre of decision-making in relation to their health and healthcare, which is also relevant in the context of medicine development (Coulter, 2011). Higgins et al. (2017, p. 33) defined PE in the context of healthcare as 'the desire and capability to actively choose to participate in care in a way uniquely appropriate to the individual, in cooperation with a healthcare provider or institution, for the purposes of maximizing outcomes or improving experiences of care'. A critical review of the current literature revealed that PE has become a widely cited term across multiple disciplines since its introduction in the 1990s, yet it remains poorly understood in terms of what it is and how to achieve it, with no unique definition (Domecq et al., 2014; Frank et al., 2015; Higgins et al., 2017). An overview of the available PE definitions in the context of healthcare and medicine development found from

the current literature is presented in ***Table 3***, which shows the multifaceted characteristics of the concept of PE across a complex spectrum of different disciplines.

In the context of healthcare, PE was, in the early twenty-first century, often conceptualized as an individual patient's behaviour to improve treatment adherence and compliance (Franklin et al., 2008; Hibbard et al., 2004; Lehman et al., 2002). This view was followed by a conceptual focus change to the enhanced relationship between patients and healthcare professionals (HCPs) to improve healthcare delivery and outcomes (Coulter et al., 2011; Davis et al., 2007; Simpson et al., 2004). In recent years, PE has increasingly been conceptualized as interactions, active partnerships, and co-creation processes, which draw on the changing perception that patients are co-creators of their health rather than passive recipients of healthcare services (Barello et al., 2012; Bright et al., 2015; Carman et al., 2013; Domecq et al., 2014; Frank et al., 2015; Higgins et al., 2017) (see ***Table 3***).

In the context of medicine development, Boudes et al. (2018) explored the meanings of PE through a qualitative survey with healthcare stakeholders, which concluded that meaningful PE in medicine development should be based on multi-stakeholder collaboration to enable patient-focused medicine development (see Table 3) and observed:

> 'there was little consensus on stakeholder expectations and roles. … no stakeholder has a clear view on how to meaningfully engage with patients; … a structure and guidance for PE is urgently required. … Effective collaboration requires consensus on roles, responsibilities and expectations to synergize efforts to deliver meaningful PE in medicine development life cycle.' Boudes et al. (2018, p. 1)

Furthermore, it was emphasized that the theoretical core of the concept of PE from a value-creation perspective remains largely unexplored but are urgently needed in terms of

what kind of value, for whom and how value could be co-created within PE in medicine development (Carman et al., 2013; Hoos et al., 2015; Lowe et al., 2016). This identified gap in the knowledge warrants further research to provide theoretical clarity and inform practice (Boutin et al., 2017; Perfetto et al., 2017) and justifies the research objectives and research questions of the present study (see Section 1.2). The current body of knowledge relating to PE in the context of healthcare and medicine development is discussed further in the next sections, situating the present study, and defining the theoretical perspectives to address the research questions.

Table 3 Overview of PE definitions in the context of healthcare and medicine from literature review

Literature	Study type	Discipline	Definition of the concept of PE in the context of healthcare and medicine development
Lehman et al., 2002	Scholarly article	Healthcare Services	Engagement as individual's behaviours in terms of *adherence to drug prescription* and as a key component for *high-quality* healthcare services
Simpson et al., 2004	Empirical study	Clinical Practices	Engagement is a factor which enables *patient alliance* with clinicians and to *enhance the recovery experience*
Hibbard et al., 2004	Empirical study	Healthcare Services	Engagement as a *behavioural activation* related to healthy behaviours and positive health outcomes
Davis et al., 2007	Theoretical research	Clinical Practices	Engagement as a key component to foster *patient-centred* medical approach
Franklin et al., 2008	Empirical study	Public Health	Engagement as a *cognitive, behavioural, emotional, and social* construct which fosters patient's self-management
Coulter, 2011	Scholarly article	Public Health	Engagement as a factor to *enhance relationship* between patients and healthcare providers, to *promote active patient involvement* and *strengthen their influence on healthcare decisions* on both individual and collective levels
Barello et al., 2012	Systematic review	Healthcare Services	Engagement as *interaction* between individual (cognitive, emotional, behavioural), relational (patients – HCPs) and organisational (context, processes, culture, etc.) levels
Carman et al., 2013	Scholarly article	Healthcare System	Engagement as *active partnership between patients and healthcare professionals* across healthcare system – direct care, organisational design and governance and policy-making – to improve health and healthcare
Domecq et al., 2014	Systematic review	Healthcare Research	Engagement as *active involvement of patients as partner and advisor* along the healthcare research
Bright et al., 2015	Theoretical research	Healthcare Services	Engagement as a *co-constructed* process and state. It incorporates a process of gradually connecting with each other and/or a therapeutic programme, which enables the individual to become an active, committed, and invested collaborator in healthcare.
Frank et al., 2015	Theoretical research	Health Economics	Engagement as *reciprocal relationships, co-learning, partnership, trust, transparency, and honesty* processes between patients and researchers to *promote patient-centred outcome* research
Higgins et al., 2017	Systematic review	Healthcare Services	Engagement as the *desire and capability* to actively choose to *take part* in care in a way uniquely appropriate to the individual, in *cooperation* with a healthcare provider or institution, to maximise outcomes or improve *experiences* of care
Boudes et al., 2018	Empirical study	Biomedical Science	Engagement as meaningful means to best *capture patients' need* to enable *patient-focused medicine development* based on *multi-stakeholder* collaboration

2.3 Patient engagement in the context of healthcare

Healthcare covers all activities and efforts made to promote, restore or maintain health with the involvement of multiple stakeholders through a healthcare system (WHO,

2006). Pharmaceutical companies (PHARMA), as healthcare service-providers operating in the healthcare ecosystem, contribute to improvements in healthcare by offering medicinal products and services for patients and, thus, the expectations around healthcare have a significant influence on the strategy and operations of the PHARMA in their medicine-development activities (Croft & McLoughlin, 2015; Lowe et al., 2016). In the context of healthcare, PE is widely acknowledged as crucial in improving healthcare quality and patient health outcomes and, consequently, reducing healthcare costs. This notion is supported by a broad range of health, academic and management literature (Carman et al., 2013; Davis, Jacklin, Sevdalis & Vincent, 2007; Domecq et al., 2014; Frank et al., 2015; Franklin, Greene, Waller, Greene & Pagliari, 2008; Hibbard & Mahoney, 2010; Higgins et al., 2017; Hoos et al., 2015; Smith et al., 2016). However, despite the increasing prominence of the concept of PE in healthcare settings, the lack of evidence-backed theoretical foundation and organisational dimension are recognised and considered to be crucial gaps in knowledge which could hinder the wider adoption of this concept in practice (Barello, Graffigna & Vegni, 2012; Carman & Workman, 2017; Hoos et al., 2015). According to these scholars, PE is a fragmented concept across multiple disciplines with no unique definition within healthcare. Moreover, little attention has been paid to understanding the intrinsic nature of PE in the research and it remains, thus, conceptually underdeveloped (Barello et al., 2012; Davis et al., 2007; Franklin et al., 2008; Hibbard, Stockard, Mahoney & Tusler, 2004; S. K. Smith et al., 2015).

A review of the literature shows a progressive shift in the conceptual focus of PE in the context of healthcare over the past decades: (i) from 2002 to 2005, a focus on the mental health context shaped the conceptualization of PE as forming an alliance between patients and physicians to improve treatment effectiveness (i.e., concerning *patient activation*, *compliance and adherence*) (Eliacin et al., 2018; Laurance et al., 2014; Millar, Chambers &

Giles, 2016); (ii) from 2006 to 2011, a more organic patient care focus has shaped the conceptualization of PE in terms of developing disease-specific self-management behaviours (i.e., concerning *patient empowerment and participation*) (Barello et al., 2012; Franklin et al., 2008; Han, Scholle, Morton, Bechtel, & Kessler, 2013; Koh, Brach, Harris & Parchman, 2013); and (iii) from 2012 to present, an increasing focus on patient-centred medicine development has moved the conceptualization of PE in the direction of incorporating patient value and VBM into the biomedical sciences with participation from multiple disciplines (i.e., concerning *patient involvement and engagement*) (Bae, 2015; Domecq et al., 2014; Higgins et al., 2017; Kelly et al., 2015; Marzorati & Pravettoni, 2017). The aforementioned findings support the statement that the conceptualization of PE has been deeply affected by the historical context, theoretical perspectives, and the disciplinary domains where the concept of PE is used, thus suggesting the need for an in-depth understanding of the concept in the specific context of use from multiple stakeholder perspectives (Barello et al., 2012; Barello, Graffigna, Vegni & Bosio, 2014). Patients' perspectives of their engagement are considered particularly relevant to understand what this concept means to patients, in order to assess all aspects of PE in the specific context of use (Barello et al., 2012; Carman et al., 2013; Duffett, 2017; Kelly et al., 2015).

The publications identified from the current literature which offer a definition of the concept of PE (see ***Table 3***) show clearly the multidimensional characteristics of the concept of PE from different disciplinary perspectives and the shift of the conceptual focus over time. Therefore, a contemporary understanding of PE, including the 'what and how' in the specific context of use is considered critical to develop theoretical foundations for this concept (Barello et al., 2012; Carman et al., 2013; Frank et al., 2015). Responding to the need to understand this complex phenomenon holistically, Barello et al. (2012) suggested investigating the concept of PE at three different levels for further research – individual,

organisational, and societal – in order to better understand the multiple interactions among stakeholders in the context of use. A similar proposal for research was made by Carman et al. (2013) to examine the concept of PE on the level of the patient (i.e., the individual level concerning the belief in the patient's role, health literacy, education, cognitive, emotional and behavioural factors), the organisation (i.e., the relational level regarding process, practices and culture) and society (i.e., the social level pertaining to social norms, regulations and policy). Despite the different terms used, these two models are comparable and facilitate a structured understanding of the key components and influencing factors in PE along a patient engagement continuum model (Barello et al., 2012; Carman et al., 2013), which are put together by the author and illustrated in ***Figure 2.***

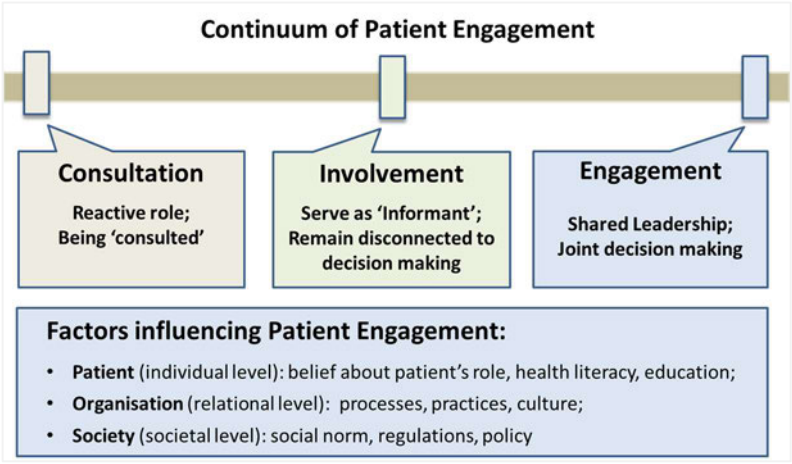

Figure 2*: PE continuum and influencing factors in the context of healthcare (Barello et al., 2012; Carman et al., 2013)*

According to this PE continuum model, depending on the information flow, patients' role and decision power, PE is described at the lower end of this continuum as consultation, which means that patients passively receive information and are asked for their opinion, but have limited power in the decision-making. At the higher end of the PE continuum, PE is considered as true engagement, with patients having shared leadership and joint decision-making power. Patient involvement is depicted as the in-between stage along the continuum where patients serve as informants and/or advisors but remain disconnected from decision-

making (Barello et al., 2012; Carman et al., 2013). The present study focuses on patient engagement (characterised as shared leadership and joint decision-making) rather than patient consultation (in which patients have a reactive role) or patient involvement (in which patients serve as informants) according to this PE continuum model. Furthermore, the present study builds on this model to explore the concept of PE in medicine development at the level of the patient, the organisation (i.e., PHARMA) and society (Barello et al., 2012; Carman et al., 2013), because this PE continuum model helps us to understand the concept of PE from different stakeholders' perspectives at different levels. In so doing, it allows the differences and similarities in these perspectives to be revealed and thus, facilitating a holistic understanding of PE in medicine development. Another strength of this PE continuum model is its consideration of influencing factors which may present the contextual influences on the concept of PE at the level of patient, organisation, and society, which are highly relevant in the application of this concept in practice. Therefore, the present study follows the line of thought developed in this PE continuum model by Barello et al., (2012) and Carman et al., (2013) to explore the concept of PE in medicine development. The world view presented in the model, of seeing a concept as a pluralistic phenomenon with multiple constructed meanings influenced by contextual factors, resonates with the researcher's own social constructivist ontological stance (for further discussion, see Section 3.2) which postulates the existence of multiple realities and socially constructed meanings in complex social phenomena (Bryman, 2016; Creswell, 2014). Consequently, the considerations derived from this PE continuum model are informative in guiding the thematic analysis of the literature and the interviews in terms of the coding and data analysis processes, because they allow a more comprehensive yet structured account of the concept of PE from the respective perspectives grounded in data (discussed further in Section 3.6). Comparing and contrasting the meanings of PE in medicine development from different stakeholders'

perspectives was suggested to be a helpful approach in arriving at a consensus definition of PE in medicine development, which is expected to be built on the understandings of multiple stakeholders (Boudes et al., 2018; Boutin et al., 2017).

Furthermore, the last decade has witnessed a change in the perception of healthcare from a 'product' offered by the healthcare system to a 'service' which is co-created by healthcare professionals (HCPs) (including PHARMA) together with patients (Batalden et al., 2016; Bright et al., 2015). Recognition of this essential co-creative characteristic of healthcare as a service is fundamental in the conceptualization of PE from the theoretical perspectives of VBM, VCC and SDL, since they are all linked to the theoretical principles of customer value, customer centricity, and the customer as value co-creator in companies' interactions with customers (Davis, Gourdji, Rhoads & Schrimpf, 2016); therefore, adopting a value-creation perspective based on VBM, VCC and SDL could offer relevant and novel perspectives for a deeper understanding about *what* and *how* questions regarding PE in medicine development, which was considered a critical knowledge gap in the current literature (Boutin et al., 2017; Frank et al., 2015; Lowe et al., 2016).

As identified from the literature review, the development focus of the concept of PE has, since 2012, been shifting from the healthcare domain (where PE has become widely established over past decades) to the biomedical medicine development domain (where PE is an emerging phenomenon in response to the paradigm shift to VBM in the healthcare environment) (Boudes et al., 2018; Domecq et al., 2014; Frank et al., 2015; Higgins et al., 2017). The increased attention given to the PE phenomenon in the context of medicine development is considered to have been triggered by increased societal pressure to improve healthcare outcomes through engaging with patients, who have gained significant power and autonomy over their health and healthcare in the past decade (Barello et al., 2015; Chiauzzi et al., 2016; Graffigna, Barello & Triberti, 2016; Newman & Vidler, 2006). Operating as

healthcare service providers in a healthcare environment, PHARMA needs to adjust their medicine development strategies and operations to align with the changing expectations of their customers – both patients and the healthcare system – in order to generate sustainable value and maintain competitiveness (Blasimme & Vayena, 2016; Bonchek & France, 2016; Boote, Telford & Cooper, 2002; Brett et al., 2014; Collier, 2015; Gillis et al., 2017). Most recently, the value of PE in the context of medicine development has been showcased in various empirical studies in areas including (i) the identification of research priorities (Dogba, Dipankui, Chipenda Dansokho, Legare & Witteman, 2018); (ii) understanding the disease burden and unmet medical needs (Israilov & Cho, 2017); (iii) facilitating efficient patient recruitment and study conduct (Holm et al., 2016); (iv) accelerating medicine approval and market access (de Wit et al., 2017); and (v) improving medication adherence and compliance (Egbuonu-Davis, 2017; Forbat, Cayless, Knighting, Cornwell & Kearney, 2009).

While the concept of PE has continually gained significance in the medicine development domain, scepticism persists among healthcare stakeholders surrounding the key questions of what constitutes meaningful PE in medicine development, wherein lies the value of PE and to whom, and how to realise the value of PE. These questions are strongly linked to the key components of a VCC theoretical perspective in terms of what kind of value and for whom (Value), with what kind of resources (Co-) and by what kind of mechanism (Creation) (Levitan et al., 2018; Perfetto et al., 2017; Saarijarvi, Kannan & Kuusela, 2013; M. Y. Smith et al., 2016). Given the increasing significance of, and knowledge gaps around, PE in the context of medicine development, a more focussed systematic literature review of PE in the medicine development domain was conducted to identify the core themes of PE in medicine development discussed in the literature, to inform the adoption of an initial theoretical perspective appropriate for this study, as discussed further in the next sections.

2.4 Patient engagement in the context of medicine development

According to the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP), the discipline of pharmaceutical medicine development is defined as 'the medical scientific discipline concerned with the discovery, development, evaluation, registration, monitoring, and medical aspects of marketing of medicines for the benefit of patients and the health of the community' (Dubois et al., 2016, p. 2). In line with this scope and definition of the developmental activities of pharmaceutical medicine development, the present study explores the concept of PE along with the full medicine development lifecycle covering the areas of research and development, regulatory policy and approval, health technology assessment (HTA) for market access, commercialisation, and marketing. Recognising that pharmaceutical medicine development is a complex social process involving multiple actors (i.e., patients, PHARMA, regulators) it sets out a broader social context in which to explore the PE phenomenon from the perspectives of relevant stakeholders with the aim of achieving a consensus understanding which is otherwise missing within both the literature and practice (Hoos et al., 2015; Lowe et al., 2016; Boutin et al., 2017).

A systematic literature search for PE in the context of medicine development (covering the domains of research and development, regulatory policymaking, and approval, HTA for market access, commercialization and marketing) between 2012 and 2019 identified 156 eligible articles (thereof, 10 studies, 32 systematic reviews, and 114 scholarly articles) (for the literature selection, see ***Figure 4*** in section 3.5.1). The starting point of 2012 was chosen based on the findings from the literature that this was a turning point, where the conceptualization of PE shifted towards a value-based perspective (Higgins et al., 2017; Kelly et al., 2015; Marzorati & Pravettoni, 2017) which is most relevant to the research objectives of the present study. The core literature (27 articles), which offers a theoretical

discussion of the components of PE in medicine development, is described in ***Annex 1***. The limited number of publications on the conceptualization of PE found in the context of medicine development suggests the nascent nature of academic research in this field, in contrast to the much larger volume of publications regarding PE in the context of healthcare (see discussion in Section 2.3). The relevant articles concerning PE in medicine development are discussed in this section concerning the research questions of the present study to devise initial theoretical perspectives for the present research.

Traditionally, medicine development and commercialization by PHARMA follows the goods-dominant logic (GDL), with medicine's efficacy and safety profile in the foreground to measure the medicine's therapeutic value in the treatment of diseases or disorders (Batalden et al., 2016; Tommasetti et al., 2015). Regulators and physicians (HCPs) are regarded as the key stakeholders by PHARMA for the purposes of medicine approval and prescription, respectively. They also share the same scientific perspectives and language as PHARMA about medicinal product evaluation, that is, they focus on efficacy and the safety profile of the medicine to assess the scientific value (Armstrong et al., 2017; Burns et al., 2014). The patient value has, to date, little relevance or meaning in the context of medicine development and evaluation (Dewulf, 2015; du Plessis et al., 2017; Duffett, 2017). However, increasing patient empowerment and the paradigm shift towards VBM in the last decade have fundamentally changed the nature of the medical encounter 'from a charity model (where resources, knowledge, and decisions are almost all on the provider side) to a partnership model (where both parties bring in and share resources, knowledge, and decisions towards common objectives*'* (Dewulf, 2015, p. 10). Consequently, the ultimate purpose of medicine development is changing from delivering super-medicine as a product to improving patient health as a service (M. M. Brown & Brown, 2013; Crawford et al., 2017; Deloitte, 2016; PhRMA, 2016; Porter, 2010; Stegemann, Ternik, Onder, Khan & van Riet-

Nales, 2016). Following the above line of thought, medicines as goods are the distribution mechanism for healthcare service provision according to service-dominant logic (SDL), a notion introduced in the marketing domain by Vargo and Lusch (2004), who claimed that value is fundamentally derived and determined in its use by customers instead of in the firm's output in the form of goods or products. Following SDL principles, engaging with patients to gain a deeper understanding of their disease burden and unmet medical needs is now becoming of the utmost importance for PHARMA in order to deliver optimum patient value as a medical service-provider (Kirwan et al., 2017; Pushparajah, 2018). Patient value is therefore to be put at the centre of the medicine development endeavour (Boutin et al., 2017; Crawford et al., 2017; Duffett, 2017). Furthermore, the strategic imperative of patient-centricity associated with PE in medicine development has been recently acknowledged and emphasised in the PFDD initiative launched by the Food and Drug Administration (FDA, 2018b) and European Medicines Agency (EMA, 2014) from a health authority (HA) perspective. Through these PE initiatives for patient-centric medicine development, both the FDA and EMA supported the concept of PE with an emphasis on patient value in the context of medicine development through providing regulatory guidelines for the pharmaceutical industry to actively engage with patients (EUPATI, 2016a, 2016b, 2016c, 2016d, 2016e; FDA, 2016, 2018a). FDA (2018b) highlights PE in the context of medicine development by emphasizing that:

> 'Patients should be meaningfully involved throughout the medical product development process - not only as study subjects but as partners. … Patients are experts in their own experience of their disease or condition and the ultimate consumers of medical products. The collection of patient experience data is important

because it provides an opportunity to inform medical product development and enhance regulatory decision making to better address patients' needs.' (p.12)

Following these PE-related regulatory guidelines from the FDA and EMA, PHARMA needs to integrate PE into its existing medicine development processes, which have not traditionally included the patient voice (Bright et al., 2015; Dewulf, 2015). The new PE requirements in medicine development, therefore, pose a significant challenge (and also an opportunity), requiring PHARMA to make changes in their strategy, culture and operations to meet the regulatory expectations and, furthermore, to capture the opportunities and benefits offered by PE in the context of medicine development (Croft & McLoughlin, 2015; Lowe et al., 2016; Messina & Grainger, 2012).

The critical literature review revealed a broad consensus among scholars and practitioners that patient value should be at the heart of healthcare for all stakeholders, and considered in the medicine research and development, approval and health technology assessment (HTA) processes (Blasimme & Vayena, 2016; Carman et al., 2013; Duffett, 2017; Getz, 2015; M. Y. Smith et al., 2016). Given the significance of patient value as a key concept in the new era of VBM, PE is considered essential in the strategy and processes for PHARMA to co-create value with patients through routine interactions throughout the medicine development lifecycle (Croft & McLoughlin, 2015; du Plessis et al., 2017; Marzorati & Pravettoni, 2017; Messina & Grainger, 2012; Mitchell et al., 2017; Sacristan et al., 2016). A few literatures have addressed why PE is needed in medicine development from a value-creation perspective with the following arguments:

(i) Patients are at the core of the healthcare system and need to be actively involved in medicine development as the ultimate consumers (Carman & Workman, 2017);

(ii) Product development starts with understanding the customers' need and providing a solution to meet this need; the same holds true in the context of medicine development (Hoos et al., 2015);

(iii) PE promotes the relevance, pragmatism and feasibility of patient-centric medicine development and generates value for patients (Getz, 2015);

(iv) Patients are the beneficiaries of medical treatment and also bear the potential risks; therefore, patient value is at the heart of medical decision-making (M. Y. Smith et al., 2016);

(v) Patients can provide enormous informational assets which need to be harvested through a partnership to promote medicine development (Blasimme & Vayena, 2016); and

(vi) The re-emphasis of patient value leads to a new healthcare system organised around patients' need and emphasising PE in medicine development (Marzorati & Pravettoni, 2017).

Most of the above arguments in favour of PE in medicine development draw on the agreement that patients are consumers and experts in their medical treatment (Carman & Workman, 2017). Therefore, firstly, value should be determined by patients as the beneficiaries (in line with the SDL perspective) (M. Y. Smith et al., 2016); secondly, patients can co-create value with service providers through interactions (in line with the VCC perspective) (Blasimme & Vayena, 2016); and, thirdly, PE leads to improved patient value (in line with the VBM perspective) (Getz, 2015). As the aforementioned arguments suggest, the theoretical perspectives of VBM, VCC, and SDL are relevant and helpful to understand PE phenomenon in medicine development and they are, therefore, adopted as a theoretical lens to explore the concept of PE in medicine development for the present study (see detailed discussion in Section 2.5).

However, the questions of what exactly PE means and how to achieve meaningful PE in medicine development to generate benefits for patients and society were controversially discussed from different standpoints in the literature, including ethical, social justice, political, economic, legal, utilitarian, strategic, tactical, transactional, operational, organisational, cultural, cognitive, psychological, behavioural, relational, methodological and philosophical perspectives (Domecq et al., 2014; Duffett, 2017; Getz, 2015; Kelly et al., 2015; Lowe et al., 2016; Richard et al., 2017; M. Y. Smith et al., 2016). These findings demonstrate further the multi-reality characteristics of the PE phenomenon which depends on theoretical perspectives and context of use. While this insight is in line with the social constructivist stance I have adopted in the present study, a clear description of the theoretical perspectives and context to frame the research is nevertheless important in setting out the research foundation (Bryman, 2015).

Drawing on the patient engagement continuum model (as discussed in Section 2.3, see ***Figure 2***) from Barello et al. (2012) and Carman et al. (2013), an initial literature analysis was performed to synthesize current understandings of PE in medicine development on three different levels: (i) the patient level, (ii) the societal level, and (iii) the PHARMA (or organisational) level. This initial literature review helped provide an understanding of the current body of knowledge and its limitations and identified research issues associated with PE in medicine development, which are informative in situating the present study within the current literature and devising appropriate theoretical perspectives as an analytical lens.

From the perspective of the individual patient, drawing on the patient's experiential knowledge of living with a condition and the positive cognitive, psychological, behavioural and emotional effects that effective PE could offer, Kirwan et al. (2017) developed a set of guiding principles for effective PE implementation based on three real-life examples. These guiding principles are establishing supportive policy; recognising partnership; adhering to

respect, trust, reciprocity, and co-learning; addressing training needs; and planning resources in advance. Despite its contribution to existing knowledge, in terms of addressing comprehensive practical aspects of PE in medicine development, this empirical study from Kirwan et al. (2017) was limited by its exploratory nature, based on three case examples within the narrow scope of patient-centred outcome research (PCOR). Similarly, Mitchell et al. (2017) suggested in a scholarly article that PE could facilitate a better understanding of patients' needs and contribute to the development of better medicines, thus promoting a genuine and trustful partnership between patients and PHARMA. This claim resonates further with the suggestions of Hahn et al. (2017) and Marzorati and Pravettoni (2017) that PE promotes delivering improved patient value in terms of positive outcomes, safety, satisfaction, accessibility and affordability which are the core values of the healthcare system. The data in these two studies were generated from workshops and interviews with the patient community and selected pharmaceutical executives and provided valuable insights about the perceived value of PE in medicine development to practitioners (Hahn et al., 2017; Marzorati & Pravettoni, 2017). However, both studies were limited by the absence of a clearly described method for data analysis and related theoretical foundations.

From a societal standpoint, the National Institute for Health and Clinical Excellence (NICE) has drawn on social value judgement principles (covering moral, distributive and procedural justice) as complementary principles to scientific value judgements in its healthcare and medicine regulation, which is decided from a utilitarian perspective, aiming to maximise the health outcomes of society as a whole through the optimised allocation of resources (NICE, 2015). The contribution of PE in medicine development to the improvement of healthcare value has been widely recognised and substantiated in robust evidence in the literature from ethical, social justice and philosophical standpoints (Carman & Workman, 2017; Crawford et al., 2017; Perfetto & Oehrlein, 2015; Getz, 2015).

Furthermore, various articles have addressed the ethical, social and legal (ESL) issues related to the implementation of PE in the context of medicine development (such as data privacy and protection, patient's autonomy and conflicts of interest) and the regulatory and methodological gaps which merit further investigation (Boutin et al., 2017; Domecq et al., 2014; Duffett, 2017; Pushparajah, 2018; Richard et al., 2017; H. Wilson et al., 2018). The majority of these publications are theoretical research, based on literature reviews, except the empirical study conducted by Duffett (2017), which draws on evidence generated from real-life PE examples from rheumatology and thromboembolism research and offers a practical account of PE application and the potential impacts of PE in medicine development. Nevertheless, this study also acknowledged the varied understandings of what PE means and the challenges in measuring PE impacts, which warrant further research to guide effective PE application and justify the time, cost and effort associated with PE initiatives in medicine development (Duffett, 2017).

From an organisational perspective, various scholars have discussed why PE is important in medicine development focussing on the interactions between patients and PHARMA. Hoos et al. (2015) argued in a scholarly article that, in every industry, product development starts with understanding the customer's need and then providing a solution to meet this need, which also holds true for medicine development in the pharmaceutical industry, i.e., meaningful PE can contribute to improved medicine development outcomes. In a scholarly article, Croft and McLoughlin (2015) discussed the link between patient value and the value for PHARMA, drawing on the triple aims of the pharmaceutical industry: innovation, value-creation and financial return on investment (ROI). They argued that key performance indicators (KPI) for the measurement of PE success are deemed necessary to justify the PE investment in medicine development (Croft & McLoughlin, 2015). However, before developing measurement metrics for PE, a conceptual PE model with defining

components is necessary which is still lacking in the current body of knowledge. Lowe et al. (2016) examined the status quo concerning PE in medicine development practices, based on interviews with six senior leaders in the pharmaceutical industry and four patients. The study highlighted that PHARMA need to demonstrate medicine's therapeutic value relative to the outcomes experienced by patients; and patients' voices should be integrated into the medicine development life-cycle in assessing the benefits and risks of medicine (Lowe et al., 2016). Despite its contribution to knowledge in rendering an account of current practical understandings of PE in medicine development from relevant stakeholders' perspectives, this study was limited by its lack of description about the data analysis method, theoretical perspective, and narrow focus in addressing the current PE issues surrounding drug development at PHARMA. Additional arguments supporting PE in medicine development were offered by Blasimme and Vayena (2016) and M. Y. Smith et al. (2016) in scholarly articles, who suggested that patients can provide valuable information that needs to be harvested through a partnership to promote improved medicine research. Insightfully, the claims of these two articles linked the value of PE on the individual patient level (following the patient value principle) to the societal level (following the utilitarian and social justice principles), which further emphasized their interdependence and the importance of balancing both perspectives in exploring PE in medicine development.

Recently, studies have increasingly begun to address *how* to include PE in medicine development from an organisational perspective. Messina and Grainger (2012) proposed a collaboration model between PHARMA and patient advocacy groups to introduce the patient voice to health technology assessment (HTA). The study used semi-structured interviews with thirteen HTA officials and four patient advocacy groups and proposed a comprehensive framework to enhance PE in the HTA processes, with rich account of the meanings given to the PE based on interviewees' narratives (Messina & Grainger, 2012). However, this study

focussed only on HTA processes and is, thus, limited by the narrow scope of the research. Drawing on a VBM perspective, Kelly et al. (2015) suggested in a scholarly article that scientific methodologies in medicine development are largely laden with unacknowledged value. Thus, patient value and scientific evidence should go hand-in-hand in biomedical research, in line with claims that the development of a common understanding regarding PE in medicine development is crucial in allowing value co-creation (VCC) by all healthcare stakeholders (Duffett, 2017; Sacristan et al., 2016; Yeoman et al., 2016). Accordingly, developing a PE conceptual framework in medicine development, through the integration of multi-stakeholder viewpoints, was considered to be urgently needed to achieve an aligned understanding of PE in medicine development (Bloom et al., 2018; Boudes et al., 2018; Frank et al., 2015).

As can be seen from the above-mentioned views, these multifaceted debates reflect the high level of societal interest in, and the enormous expectations of, this research topic. The concept of PE in medicine development has been designated the blockbuster drug of the century, expected to solve multiple healthcare problems (Dentzer, 2013; Kish, 2012). On the other hand, it also mirrors the different expectations, priorities, and conflicts of interest among healthcare stakeholders (i.e. patients, regulators and PHARMA), who often differ in their understandings of value, and how it can be created and measured within PE in medicine development (Boudes et al., 2018; Perfetto et al., 2017). Furthermore, the lack of theoretical underpinnings (i.e., the theoretical foundations upon which to understand a phenomenon and address the related research issues) concerning PE in medicine development, as discussed above, prohibits a more complete and insightful understanding of this phenomenon among its practitioners. Despite the practical eagerness in gathering experiences and factual knowledge relating to this phenomenon by multiple stakeholders within multiple contexts (e.g., healthcare services, policymaking, HTA, patient self-management) over decades, the

theoretical core of the concept of PE in medicine development remains vague and unexplored (Domecq et al., 2014; Boutin et al., 2017). For example, no aligned definition of PE in medicine development is available to address the meaning of this concept (Hoos et al., 2015), and a PE methodological framework is lacking in guiding practical applications of this concept (Lowe et al., 2016). Therefore, the theoretical development of this new PE phenomenon in medicine development (i.e., to articulate the essence of practical knowledge and provide a broader framework integrating existing professional knowledge to address *what* and *how* questions about this concept) is deemed both necessary and essential to further advance this concept in both theory and practice.

Moreover, these underlying value debates concerning the concept of PE in medicine development suggest an essential theoretical link to the theories of value-based medicine (VBM), value co-creation (VCC), and service-dominant logic (SDL), which all build on the key concepts of value, customer (or patient) value and customer (or patient) engagement. Furthermore, these theoretical perspectives share a common belief that value should be co-created with customers and measured from the perspective of the customers as beneficiaries (as discussed in Sections 2.3 and 2.4), which could help to explore the research questions about what kind of value for whom, with what kind of resources and mechanism concerning PE in medicine development (see Section 1.2). Given their explanatory power and intrinsic relevance to the concept of PE in medicine development, an initial theoretical perspective based on VBM, VCC and SDL is therefore adopted as an analytical lens to conceptualize PE in medicine development in the present study, as further justified in the next sections.

2.5 Theoretical perspectives

As revealed by the literature review and discussed in the previous sections, VBM, VCC and SDL have been identified as relevant theoretical foundations underlying the concepts of patient value, patient engagement and healthcare value in the context of medicine

development (M. M. Brown & Brown, 2013; du Plessis et al., 2017; Hoos et al., 2015; Kelly et al., 2015; Lowe et al., 2016; Porter, 2010; Yeoman et al., 2016). These theoretical perspectives were thus elaborated upon serving as a lens for the conceptualization of PE in medicine development in the present study. A detailed discussion of the key aspects of the initial theoretical perspectives is presented in this section regarding (i) its relevance to the concept of PE in medicine development; (ii) its relationship to other related concepts of PE in medicine development; and (iii) it's use in the present study to address the research questions.

2.5.1 Value-based medicine (VBM)

Twenty years ago, evidence-based medicine (EBM) was considered a ground-breaking movement in clinical decision-making, combining the best available scientific evidence with clinical expertise, and a revolutionary application of science in clinical practice addressing the paternalistic approach of the physicians (Marzorati & Pravettoni, 2017). Drawing on a positivist paradigm, EBM has stimulated the debate between researchers and clinicians by regulating practical medical knowledge with quantitative findings and guidelines, thus attempting to bridge the evidence gap between biomedical science and clinical practice (Isaac & Franceschi, 2008). However, EBM still addresses healthcare issues from a conventional biomedical stance which focuses on controlling the disorder rather than putting patients at the centre of medical treatment (Isaac & Franceschi, 2008; Marzorati & Pravettoni, 2017). Consequently, the healthcare value definition from an EBM perspective is the improvement of physiological conditions, measured in terms of clinical efficacy, effectiveness, safety, benefits, and risks of the medicines (Marzorati & Pravettoni, 2017). The notion that health status is not only determined by the survival or absence of disease but is also influenced by the subjectivity of patient value is, however, ignored from the EBM perspective (Riva & Pravettoni, 2016).

Several years later, the concept of value-based medicine (VBM) was introduced by Brown et al. (2003), emphasizing patient value in clinical decision-making, and complementing EBM by adding patient preference and utility components, thus significantly stimulating the paradigm shift from evidence-based to value-based healthcare (Bae, 2015; G. C. Brown et al., 2003; K. Fulford, 2004). The VBM approach to healthcare has been defined by Brown et al. (2003, p. 1) as 'the practice of medicine incorporating the highest level of evidence-based data with the patient-perceived value conferred by healthcare interventions for the resources expended'. The individual aspect in terms of patient value is now included and has become the critical core component in healthcare outcomes from a VBM theoretical perspective (Bae, 2015; Riva & Pravettoni, 2016). Sackett et al. (2000, p. 1) define patient value as 'the unique preferences, concerns and expectations each patient brings to a clinical encounter and which must be integrated into clinical decisions if they are to serve the patient'. From a patient's perspective, the burden of illness is not limited to the conditions caused by the disease; it is also important to consider the health-related quality of life (HrQoL) aspects associated with medical treatment, a subjective multi-dimensional measure including physical, psychological, emotional and occupational functioning, individual behaviour and attitude, social interaction, personal experience, culture, beliefs and somatic sensations (Fulford, 2004; Post, 2014). Drawing on VBM theory, HrQoL is frequently used as a parameter to measure health beyond the presence of disease, thus representing the patient value of a medical treatment beyond the treatment effect itself (M. M. Brown & Brown, 2013; Riva & Pravettoni, 2016). The VBM perspective, with its emphasis on patient value, conforms with the much-quoted definition of health by the World Health Organization (WHO) as 'a state of complete physical, mental and social well-being, not merely the absence of disease or infirmity' (WHO, 2006, p. 1). Based on this broader understanding of the concept of health, Porter (2010, p. 2477) further developed the notion

of VBM by emphasising that 'achieving high value for patients must become the overarching goal of health care delivery, with value defined as the health outcomes achieved per dollar spent. This goal is what matters for patients and unites the interests of all actors in the system'. Porter (2010, p. 2477) also proposed a hierarchy of health outcome measures, following the principle that 'value should always be defined around the customer, and in a well-functioning health care system, the creation of value for patients should determine the rewards for all other actors in the system'. These VBM principles are fully aligned with the theoretical propositions of VCC, which allows the integration of the providers' market offering with the customer's fulfilment of value through interaction and engagement (Prahalad & Ramaswamy, 2004); and SDL, in which value is always determined by the beneficiary, and the customer is always the value co-creator (Vargo & Lusch, 2008). Therefore, a theoretical lens based on VBM, VCC and SDL is consistent and relevant in exploring the phenomenon of PE in the context of medicine development.

While VCC and SDL could offer general theoretical explanations for customer (or patient) engagement, and are established marketing and management theories widely used across multiple industries (Skaržauskaitė, 2013; Terblanche, 2014; Tommasetti, Troisi & Vesci, 2015), VBM provides a specific theoretical background for the PE phenomenon in the field of medicine development, with an emphasis on value and patient value (M. M. Brown & Brown, 2013; Porter, 2010). In recent years, VBM has significantly changed healthcare into a more service-oriented, customer-centric and value-driven environment, sharing a theoretical core with VCC and SDL as observed in other industries (M. M. Brown & Brown, 2013; K. Fulford, 2004; Isaac & Franceschi, 2008; Marzorati & Pravettoni, 2017; Sackett et al., 2000; M. Y. Smith et al., 2016). The above discussion provides a strong argument to support the theoretical relevance of VBM, VCC and SDL in exploring PE in

medicine development, and they are, therefore, justified as appropriate theoretical perspectives for the present study.

Operating in a healthcare environment, PHARMA is involved in the research and development (R&D), registration and commercialization of medicinal products. Its strategy and operations as of today, however, still rely on the conventional clinical efficacy and safety concepts with a focus on the treatment of disease and the therapeutic value of medicines (FPM, 2011). Conventionally, pharmaceutical medicine development relies mainly on the judgement of accredited medical experts (i.e., physicians, scientific investigators, clinicians, PHARMA and regulators, who can be collectively classified as healthcare professionals) regarding the benefits and risks profile of a medicine for regulatory approval and commercialization. Health-related quality of life (HrQoL) measures, concerning patient value, are still far from being considered the top priority in the medicine development processes of PHARMA (Carman et al., 2013; Carroll et al., 2017; Dewulf, 2015). Likewise, regulatory review and authorization of medicines by HAs follow the same efficacy and safety concepts in terms of assessing the benefits and risks related to the medicine's therapeutic value (EMA, 2016b; FDA, 2018b). Over the last decade, health technology assessment (HTA) agencies have increasingly asked for HrQoL data in making pricing and reimbursement decisions at the point of market access by emphasising PE in medicine development (Brettschneider, Lühmann & Raspe, 2011; NHC, 2016). However, the literature describes several challenges as key barriers to applying the concept of PE in medicine development: (i) uncertainty about how to identify representative and appropriate patients for PE to obtain the required inputs (Duffett, 2017; Grande, Faber, Durandc, Thompsona & Elwyna, 2014; Sienkiewicz & van Lingen, 2017); (ii) uncertainty about the patient's role in the context of medicine development, given concerns about the medical knowledge deficit of patients (Gruman et al., 2010; Hunter, O'Callaghan & Califf, 2015;

Jones, Postges & Brimicombe, 2016; Kirwan et al., 2017); (iii) a lack of evidence about the beneficial impacts of PE in medicine development (Getz, 2015; Levitan et al., 2018; Miseta, 2015b); and (iv) the need for cultural change in PHARMA and to support patients' education as prerequisites for an effective PE in medicine development (Bloom et al., 2018; Carroll et al., 2017; du Plessis et al., 2017; Hahn et al., 2017).

According to the literature, the lack of consensus about the real value of PE and what meaningful PE should look like in medicine development were frequently cited as the major reasons for PE tokenism in PHARMA, that is, making a symbolic effort to engage with patients (Buck et al., 2014; Hahn et al., 2017; Hall et al., 2018; Sieck, Hefner & McAlearney, 2017; Thomson, Murtagh & Khaw, 2005; Wong-Rieger, 2016). Given these discussions, further theoretical and practical research into the concept of PE in medicine development (e.g. what does PE mean, how should meaningful PE be implemented) is deemed necessary to address these issues and advance knowledge about PE in medicine development (Forsythe et al., 2014; L. Fulford, 2017; Goodridge et al., 2018; Hahn et al., 2017; Hurst et al., 2017; Jackson, 2016; Kendell, Urquhart, Petrella, MacDonald & McCallum, 2014; Kielmann et al., 2011). This need defined the research objectives and research questions of the present study (see Section 1.2).

In terms of advancing PE in medicine development, health economics, concerning the health technology assessment (HTA) of medicine for market access and price decisions, has made significant progress in recent years, with the introduction of various new health outcome measurement concepts around patient value – such as HrQoL, patient preference, patient-reported outcome measures (PROM) – as tools to evaluate the overall health outcome from a patient's perspective (Pitts, 2016; R. Robinson, 2013; H. Wilson et al., 2018). Gradually, patient value and VBM perspectives have further challenged traditional medicine development practices, demanding integration of patient value into the established medicine

development processes of PHARMA, with PE suggested as the answer for this demand (Basch, 2013; Bloom et al., 2018; Coons et al., 2015; DasMahapatra, Raja, Gilbert & Wicks, 2017; de Bekker-Grob et al., 2017; Hunter et al., 2015). Furthermore, regulators recently introduced PE initiatives to the medicine review and authorization processes in response to this new VBM demand. For example, the newly launched PFDD initiatives by the FDA emphasised the importance of gathering patients' perspectives in the context of medicine development, in line with VBM theory and the concept of PE, since they are all built on the same theoretical proposition that value should be created and measured around the customers - patients - as the beneficiaries (M. M. Brown & Brown, 2013; DIA, 2015; Dubois et al., 2016; EMA, 2014; FDA, 2018a; Porter, 2010).

In summary, VBM emphasizes the integration of patient value (i.e., patient experience through value-in-use) into the scientific evidence (i.e., knowledge and market offerings by PHARMA through value-in-exchange) (M. M. Brown & Brown, 2013). Following this line of thinking, PE becomes core in delivering patient value throughout the medicine development lifecycle from a VBM theoretical perspective (M. M. Brown & Brown, 2013; Porter, 2010; Saarijarvi et al., 2013). Taking these considerations into account, the VBM theoretical perspective is adopted to explore the PE phenomenon from a value-creation perspective in the present study, as it is relevant and powerful for the conceptualization of PE in the context of medicine development.

Furthermore, drawing on the wider acceptance of value co-creation (VCC) and service-dominant logic (SDL), as recognised and evidenced by a broad range of research in different fields and contexts, the concept of PE is also explored from VCC and SDL perspectives in the present study, as further elaborated and justified in the next section.

2.5.2 Value co-creation (VCC) and service-dominant logic (SDL)

Value co-creation (VCC) was first introduced in the management literature by Prahalad and Ramaswamy (2000), describing how companies and customers generate value through interaction. VCC is rooted in service-dominant logic (SDL) principles, which propose that (i) goods are a distribution mechanism for service provision; (ii) service is the fundamental basis of exchange; (iii) value is always determined by the beneficiary; (iv) the customer is always a co-creator of value; (v) the SDL view is inherently customer-oriented and relational; and (vi) all social and economic actors are resource integrators (Vargo et al., 2008). Following the principles of SDL, 'service is a perspective on value creation rather than a category of market offerings' (Edvardsson, Gustafsson & Roos, 2005, p. 118), thus emphasizing the generation of customer value through the VCC processes of customers and companies. Furthermore, Vargo and Lusch (2008, p. 145) argued that 'value is fundamentally derived and determined in use – the integration and application of resources in a specific context, rather than in exchange – embedded in firm output and captured by price'. Drawing on the SDL theoretical propositions described above, VCC assumes that customers have an active role to play in value-creation together with the company (Prahalad & Ramaswamy, 2000), thus sharing common theoretical principles with VBM theory and PE in the medicine development domain, as described in Section 2.5.1 (M. M. Brown et al., 2005; Gillis et al., 2017; Holm et al., 2016; Loeffler et al., 2013; Salimi, Epstein, Lehner & Tunis, 2012; Sartori, Steinmann, Evers & Jantzer, 2016).

Over the past decade, VCC has gained substantial attention from both marketing and management scholars, which has since been widely applied within such research domains as services sciences, innovation, and consumer research. It is, however, frequently muddled with other terms used in the practice with a different conceptual focus (Alqayed et al., 2020; Galvagno, 2014). The term 'co-production' finds its origin in the public service sector which

describes the joint production process of public offerings (i.e., goods and services) with an emphasis on citizens' active involvement and sharing of responsibility through collaboration with service providers (Brandsen et al., 2018; Dudau et al., 2019; Graffigna et al., 2020). Furthermore, 'co-production' implies an association with a GDL rooted in the industrial economy with a focus on the customer's *involvement as a resource* for the joint production of offerings together with service providers are concerned (Vargo et al., 2020). The term 'co-design' is considered to be the first step in the joint development of offerings (i.e., conceptually design and plan of new offerings) towards the 'co-production' (i.e., implementation and delivery of offerings) (Dudau et al., 2019; Elbers et al., 2021). Conceptually, 'co-design' draws upon participatory research and user-centric design principles, wherein service users are considered as important *informants to be consulted* to optimise the service design (Trischler et al., 2019; Yadav et al., 2020; Zamenopoulos et al., 2018). Together, 'co-design' and 'co-production' are considered to be two inherent core components of 'co-creation' from a VCC and SDL perspective (Ranjan & Read, 2014; Vargo et al., 2020). Additionally, drawing on the concept of 'co-production', 'co-construction' emerged as a surrogate term that shifts the conceptual focus from 'service provider and service user interaction at the micro level' (i.e., 'co-production') to a broader *service ecosystem* at the macro level (namely 'co-construction'). Within the context of the service ecosystem, 'co-construction' describes a "relatively self-contained, self-adjusting system of resource-integrating actors connected by shared institutional arrangements and mutual value creation through service exchange" (Vargo, 2020, p.12). From a service ecosystem perspective, the *lived experience* of service users will impact their engagement with a service system, so the service users will 'co-construct' their own life experience (i.e., customer value) through relationship and interactions with the service ecosystem (Andion et al., 2019; Brandsen et al., 2018). Following this line of thought, service users are adopting a

role of *shared leadership and joint decision making* (i.e., being *engaged with* and *engaged in*) to 'co-construct' a value-creating ecosystem jointly with other stakeholders (Calcagni et al., 2019; Pomey et al., 2019; Vaillancourt, 2009). Lastly, 'co-creation' is suggested as a general broader concept, one which is rooted in the service science that emphasises the joint creation of value by stakeholders and customers through collaboration within the service ecosystem, with customers having an active role to play in the 'co-design' and 'co-production' of offerings and also in the 'co-construction' of value as the ultimate overarching aims (Barile et al., 2020; Brambilla et al., 2020; Mandolfo et al., 2020).

Drawing on the wider management and marketing literature, VCC involves two key conceptual elements: Value-in-Exchange (ViE) and Value-in-Use (ViU) (Prahalad & Ramaswamy, 2000; Vargo et al., 2008). According to the SDL perspective, ViE concerns resources in the provider's sphere (market offerings by providers) used as a value foundation to facilitate the customer's fulfilment of value, whereas the value for customers is created within the ViU processes in the customer's sphere (Sandström, Edvardsson, Kristensson & Magnusson, 2008). Ranjan and Read (2014) further developed the theories of VCC and SDL through a systematic review and revealed the core defining attributes of ViE to be 'knowledge, equity, and interaction', while the key defining attributes of ViU are 'experience, personalisation, and relationship'. Next, scholars postulated that VCC among customers and service providers relies on the essential conceptual elements of 'engagement, interaction, and experience' (Bendapudi & Leone, 2003; Ranjan & Read, 2014). Furthermore, the VCC is not fully determined unless the result is used by customers in the ViU processes (Sandström et al., 2008). Saarijarvi et al. (2013) proposed another analytic approach to explore the three key theoretical constitutes of VCC in 'Value', 'Co-' and 'Creation', aiming to comprehend this theory by addressing the three key issues of (i) what kind of value for whom ('Value'), (ii) by what kind of resources ('Co-') and (iii) using what

kind of mechanism ('Creation'). This analytic approach was considered helpful in addressing the same research questions regarding PE in medicine development from a value-creation perspective and is therefore adopted in the present study (see ***Figure 3***). Lastly, in adopting an SDL view, customers are always value co-creators, and firms need to participate in the value-generating ViU processes of customers by providing market offerings through interactions (Grönroos, 2008). Put differently, value can be co-created by the providers and customers through interactions and engagement connecting the ViE (i.e. market offerings of providers) and ViU (i.e. customer's fulfilment of value) components (Grönroos, 2008; C. K. Prahalad & V. Ramaswamy, 2004; Terblanche, 2014). The theoretical core and key principles based on VCC and SDL perspectives (as discussed above) are put together by the author and illustrated in ***Figure 3.***

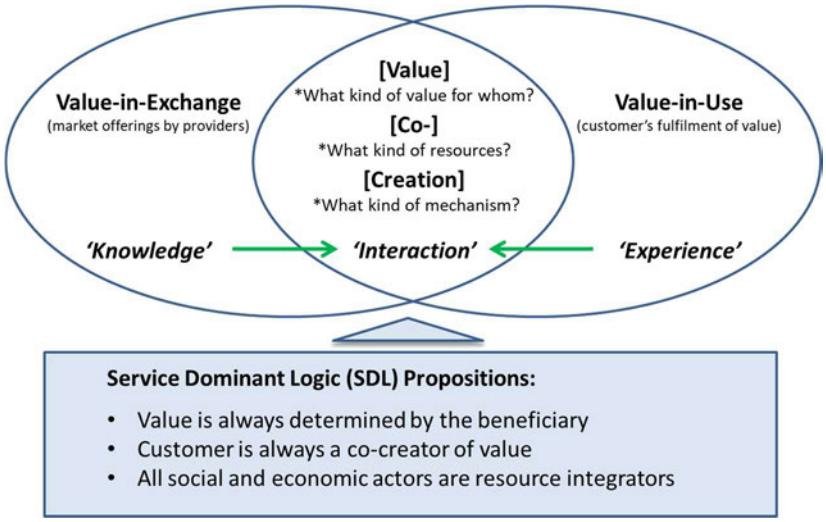

Figure 3*: VCC and SDL theoretical perspectives*
(Prahalad & Ramaswamy, 2000; Ranjan & Read, 2014; Saarijarvi et al., 2013; Vargo & Lusch, 2004)

As illustrated in ***Figure 3***, the components and principles of the VCC and SDL theories offer an insightful lens for the exploration of PE in medicine development, providing a theoretical perspective which has long been established in management and marketing principles applied across multiple industries (Galvagno & Dalli, 2014; Saarijärvi, Kannan & Kuusela, 2013; Tommasetti et al., 2015). VCC and SDL have been extensively used as a theoretical perspective through which to explore customer engagement in both

goods and services sectors, and have been widely cited and evidenced in literature as powerful theoretical concepts explaining customer engagement for value co-creation (Etgar, 2008; Fang et al., 2008; Grönroos, 2011; Payne, Storbacka & Frow, 2007; Sandström et al., 2008; Terblanche, 2014; Velamuri, Neyer & Möslein, 2011). Drawing on the theoretical foundations of VCC and SDL, customer engagement is defined in the marketing and management literature as a form of interaction, an alliance and co-production between company and customers to enhance knowledge-sharing, build trust and loyalty, thus generating positive customer experiences (Gambetti & Graffigna, 2014). Furthermore, through collaboration between customers and service providers, customer engagement has been shown to deliver customer's fulfilment of value, thus building a competitive edge for those service providers (Devasirvatham, 2012) which concur with the key principle of SDL that the customer is a key value contributor in the value-creation processes of the firm (Grönroos, 2011).

VCC and SDL theories are suggested especially powerful in exploring customer engagement in domains such as innovation (medicine development is a highly innovative endeavour), allowing companies and customers to co-create novel ideas by combining their perspectives (Grönroos, 2008). Recently, VCC and SDL principles have been increasingly used to explore PE in the context of healthcare and medicines, since this sector has moved towards being a customer-centred, service-oriented and value-driven industry with an emphasis on patients as customers of healthcare and medicines (Akhmetov & Bubnov, 2017; Auha, Bell, McLeodc & Shih, 2007; Croft & McLoughlin, 2015; Devasirvatham, 2012; Eyeforpharma, 2015; Galvagno & Dalli, 2014; Saarijärvi et al., 2013; Tommasetti et al., 2015). The well-established theoretical and practical knowledge of customer engagement based on VCC and SDL theories, which has been gained from other industries over decades, could therefore help explore the emerging PE phenomenon (equivalent to customer

engagement in other industries) in the context of medicine development (Galvagno & Dalli, 2014; Grönroos, 2011; Porter, 2010; Saarijärvi et al., 2013). Given the consensus that patients are the beneficiaries and customers of healthcare and medicines, meaningful interaction and collaboration between patients and healthcare service providers (e.g. PHARMA) could enable VCC for all parties involved, generate mutual benefits and enhance trust (Barello et al., 2012; Boudes et al., 2018; Bright et al., 2015). Furthermore, recent studies have suggested the relevance and usefulness of the VCC and SDL theoretical perspectives in understanding the PE phenomenon in the context of medicine development (Batalden et al., 2016; Duffett, 2017; Kirwan et al., 2017; Messina & Grainger, 2012).

Taking the above discussions into account, VCC and SDL have essential theoretical relevance and explanatory power for the conceptualization of PE in medicine development (du Plessis et al., 2017; Lowe et al., 2016; Smith et al., 2016; Yeoman et al., 2016). Therefore, they were adopted to explore PE in medicine development in the present research. The theoretical perspectives based on VBM, VCC and SDL theories are further discussed in the next section regarding how these perspectives are used for the conceptualization of PE in medicine development in the present study.

2.5.3 Patient engagement in medicine development based on VBM, VCC and SDL

The theoretical perspectives based on VBM, VCC and SDL were adopted as an initial theoretical lens in the present study to explore the concept of PE in medicine development from a value-creation perspective, which are closely intertwined with each other through the key constructs of knowledge, experience, and interaction (as discussed in Sections 2.5.1 and 2.5.2). These theoretical perspectives and constructs offer explanatory capacity to comprehend the multifaceted PE phenomenon from the disciplinary perspectives of medicine, marketing and management respectively (G. C. Brown et al., 2003; Porter, 2010; Prahalad & Ramaswamy, 2004; Vargo & Lusch, 2004) and are, therefore, regarded as a

useful and appropriate theoretical foundation to support the conceptualization of PE in medicine development.

Furthermore, the concept of PE in medicine development, suggested to be interlinked with the concepts of patient value and patient centricity, was argued to be a core concept connecting the VBM, VCC and SDL theories in the context of medicine development (G. C. Brown et al., 2003; Prahalad & Ramaswamy, 2004; Vargo et al., 2008). This was also reflected in the view that PE in medicine development is becoming the blockbuster drug of the century in achieving better health outcomes for patients through re-emphasizing of patient value and patient centricity (Dentzer, 2013; Kish, 2012). Further, these theoretical perspectives resonate with the overarching healthcare aim that 'achieving high value for patients must become the overarching goal of healthcare; … This goal is what matters for patients and unites the interest of all actors in the system' (Porter, 2010, p. 2477).

Taking the above discussions together, VBM, VCC and SDL theories can offer a comprehensive account of the PE phenomenon by providing a powerful analytical lens for observations, understandings, data collection and analysis from the disciplinary perspectives of medicine, management and marketing, to facilitate crisp thinking and novel insights about PE in medicine development (M. M. Brown & Brown, 2013; Prahalad & Ramaswamy, 2004; Vargo et al., 2008). Considering the explanatory power, the relevance and the interlinked nature of the theoretical perspectives of VBM, VCC and SDL, the conceptualization of PE in medicine development based on these perspectives are considered useful to address the RQs about *what* and *how* concerning PE phenomenon (see Section 1.2) and deemed as justified and thus adopted in the present study. Lastly, drawing on the above discussions, the relevant key concepts and theories associated with the concept of PE in medicine development (as discussed above), based on VBM, VCC, and SDL theoretical perspectives adopted for the present study, are provided in ***Table 4***.

Table 4: Definition of key concepts based on VBM, VCC, and SDL theoretical perspectives

Concept / Theory	Definition	Reference
Patient Value	Means the unique preferences, concerns and expectations of individual patients towards medical treatment; and positive results in patient's outcome, safety, and satisfaction at a reasonable and affordable cost	Sackett et al. (2000); Marzorati & Pravettoni (2017)
Scientific Evidence	Clinical efficacy, effectiveness, safety, benefits, and risks data of a medicine gathered from biomedical sciences and clinical practices	Isaac & Franceschi (2008) Marzorati & Pravettoni (2017)
Value-in-Exchange	Concerns the resources, knowledge, and market offerings in the provider's sphere, used as a value foundation to facilitate customer's fulfilment of value	Sandström, Edvardsson, Kristensson & Magnusson (2008)
Value-in-Use	Concerns the customer's fulfilment of value through experience, personalisation, and relationship	Ranjan & Read (2014)
Value-Based Medicine (VBM)	Means the practice of medicine incorporating the highest level of evidence-based data with the patient-perceived value conferred by health care interventions for the resources spent	M. M. Brown & Brown (2013); Porter (2010)
Value Co-Creation (VCC)	Describes occurrences in which companies and customers generate value jointly through interaction	C. K. Prahalad & V. Ramaswamy (2004)
Service-Dominant Logic (SDL)	Value is fundamentally derived and determined in use – the integration and application of resources in a specific context – rather than in exchange – embedded in firm output and captured by price	Vargo et al. (2008); Vargo & Lusch (2015)

The respective conceptual elements within these theoretical perspectives support to comprehend the PE phenomenon in the context of medicine development. For instance, the guiding questions from a VCC perspective (i.e., 'value': what kind of value for whom? 'Co-': what kind of resources? 'Creation': what kind of mechanism?) informed the development of the research objectives (see Section 1.2) and the interview guide (see ***Annex 2***) to address the identified research issues (see ***Table 2***). That is, these research questions were explicitly asked during the interviews to capture understandings and perceptions from interviewees concerning the key components of PE in medicine development from a value-creation perspective, thus establishing the direct linkage between the theoretical perspectives with the research questions and interview guide, and further informing the development of research methodology and design for the present study, which are discussed in detail in Chapter 3.

2.6 Summary

To conclude, this chapter has presented a critical review of patient engagement in the literature of healthcare and medicine development. The review elaborates upon different conceptual aspects associated with PE in medicine development. Drawing on the theories of

VBM, VCC and SDL, an initial theoretical perspective was both discussed and justified for the purposes of the present study, which serves as an analytic lens through which to explore the PE phenomenon in medicine development from the disciplinary perspectives of medicine, marking and management. Despite a considerable argumentation offered by scholarly articles to support the vital role of these theoretical perspectives to the understanding of PE phenomenon in medicine development, no study was found in the current literature to explore PE in medicine development from these perspectives. The present study aims to offer novel insights about PE in medicine development from a new value-creation theoretical perspective based on VBM, VCC, and SDL, and to expand knowledge in this field. As a result, this chapter fulfils the purposes of situating the present study within the current body of knowledge, justifying the adoption of a value-creation theoretical perspective and the originality of this thesis to close the identified knowledge gaps.

Furthermore, the initial theoretical perspectives presented in this chapter informs the development of the research questions, the research methodology and the interview guide in the present study. The link between the value-creation theoretical perspectives and the research methodology designed for the present study is elucidated in the following chapter.

3 Research methodology and design

3.1 Introduction

This chapter firstly outlines the ontological stance and epistemological paradigm which I have adopted to address the research questions in the present study. A methodological framework based on Rodgers's (1989) evolutionary concept development approach is adopted which is considered in alignment with the research objectives, the value-creation theoretical perspective, and the research paradigm. Considerations are given to the background of different approaches to concept analysis and development with regards to their strengths and limitations. Next, rationales are provided for the choice of a qualitative research method based on thematic analysis for the data collection, analysis, and interpretation in the present study. An outline of research activities covering data collection and analysis methods to address the respective research objectives are elucidated and justified. Furthermore, the trustworthiness of this qualitative study including the researcher's reflexivity is considered. Finally, considerations about ethical issues are discussed, and mitigation measures are demonstrated.

3.2 Research paradigm

The healthcare and medicine sector is a complex socio-political system that involves multiple stakeholders, including regulatory health authorities (HAs), national health insurance institutes, healthcare givers, the pharmaceutical industry as a medicine and services provider, and patients as consumers of healthcare services (Baines & de Bere, 2018; Boudes et al., 2018). Although all healthcare stakeholders claim to have a shared goal of delivering affordable, innovative medicinal products to patients, the outcomes in healthcare performance still deviate from this declared goal (WHO, 2016). In this context, PE in medicine development is considered an important factor in addressing these healthcare issues to achieve the declared common goal (Coulter, 2011; Dentzer, 2013). Within PE, the

conventional medicine development paradigm is shifting to a more service-oriented, patient-centred, and value-driven approach, triggered by technological innovations including digital health technology, precision medicine, genomics and cell therapy (Duffett, 2017). These innovative technologies have significantly reduced the information asymmetry of patients and have given patients unprecedented power in the healthcare system (Croft & McLoughlin, 2015). Consequently, this increased patient empowerment requires PE in medicine development to reflect the changing role of patients and, thus, the changing social interactions among healthcare stakeholders (Higgins et al., 2017; Lowe et al., 2016). To explore an emerging complex social phenomenon such as PE in medicine development, a qualitative inquiry based on a social constructivist ontological stance with an interpretivist epistemological paradigm is considered the most appropriate approach (Kuhn, 1970; Popper, 2004; Rodgers, 2000), as elaborated below.

Ontology is the theory of being or existence, and indicates a philosophical perspective on the nature of social reality; the two most distinct ontological positions are realism and constructivism (King & Horrocks, 2010). The natural sciences (such as biomedical research and medicine development) are primarily founded on realism, the belief that the real world can be discovered and validated by empirical data independently of individuals (Creswell, 2017). Conversely, the social constructivist views knowledge and meanings as constructed by individuals through interactions and social actions; knowledge and meaning are historically and culturally specific and often bound with relationships of power (Burr, 2003). Social constructivism contends that social phenomena and their meanings are continually shaped and accomplished by social actors; thus, our conscious interpretations construct the meanings of social phenomena (Bryman, 2015). King and Horrocks (2010) argue further that social constructivism describes the social world by offering a detailed account of specific social settings, processes, and relationships. From a

social constructivist standpoint, qualitative inquiries are considered a good means of capturing the experiences and understandings of the relevant stakeholders and of constructing insights and concepts for solutions (Bowling, 2014; Little, 1991). Drawing on the critical literature review (see Section 2.4), patient engagement (PE) in the context of medicine development was shown to be a multi-dimensional, complex, social phenomenon (Boutin et al., 2017; Hoos et al., 2015). The meanings of PE in medicine development could be multiple, depending on the individuals who may construct their understandings and meanings through different experiences and social roles (e.g., from the perspective of a patient, PHARMA or society) (Boudes et al., 2018; Carman et al., 2013). Therefore, there is no single truth regarding the concept of PE waiting to be discovered independently of the social actors; rather, a comprehensive account of the social settings, processes, roles and relationships around PE in medicine development is needed to consciously interpret the constructed meanings of such a complex, social phenomenon (Kelly et al., 2015; Lowe et al., 2016). Taking the above arguments into account, a social constructivist ontological stance is considered more appropriate for the present study in exploring the understandings and perception of a complex social phenomenon, such as PE in medicine development, based on inputs from relevant healthcare stakeholders.

Epistemology addresses the philosophical question of 'how do we know what we know' in terms of establishing what constitutes knowledge (Kuhn, 1970). There are two major epistemological paradigms in science: positivist and interpretivist (Popper, 2004). Popper (2004) argued that, in adopting a positivist paradigm, the whole is reduced to its parts or components and they are studied separately before generalization is attempted; furthermore, the researcher is considered as independent of the observed and the analysis is therefore objective and value-free. Thus, the experiences of people, their beliefs, concerns, obstacles, attitudes and values are not captured by positivist, although an understanding of

these aspects of life could potentially enrich the analysis (Kuhn, 1970). Hegde (2015) suggested that reductionism and determinism assumed by positivism impose constraints on the understanding of human affairs regarding related issues, relationships, interactions, values, attitudes, and beliefs, which play a large part in shaping the world. Abstracting the analysis of these human factors deprives us of a holistic understanding of systems. Kuhn (1970) described progress in science not as a simple line leading to the truth but rather as progress away from a less adequate concept through interactions with the world. According to Kuhn (1970), the researcher attempts to move as close to the truth as possible by enquiring and verifying within the ruling paradigms of normal science, and the process continues until traditional science is replaced by revolutionary science, making way for a new paradigm. The same principles hold true for the exploration of PE as an emerging social phenomenon in the context of medicine development, which needs to be understood within the new value-based medicine (VBM) paradigm to advance knowledge (Bowling, 2014; Bright et al., 2015; Perfetto et al., 2017). Following the argument that individuals may construct the meaning of PE in medicine development based on their specific social role and individual experiences through social interactions, the researcher will need to grasp the subjective meanings that respective stakeholders attach to the concept of PE to interpret the constructed meanings. Therefore, an interpretivist epistemology was considered more appropriate for exploring this emerging social phenomenon through qualitative inquiries, rather than a positivist statistical verification based on large empirical samples (Maxwell, 2012). Since PE, in the context of medicine development, is an emerging social phenomenon, few theoretical understandings of this phenomenon were available in the literature (Carman et al., 2013; Domecq et al., 2014). Consequently, a more exploratory approach based on qualitative inquiries was deemed appropriate to address the research objectives in the present study (see Section 1.2), where the emphasis is placed on understanding the concept of PE in medicine development,

grounded in data from literature and interviews (see research objectives 1 and 2 in the present study) and to generate theory inductively based on these understandings (research objective 3 in the present study). I, therefore, adopted an interpretivist epistemological paradigm for the present study, which allowed the gathering of fresh insights through investigations with relevant healthcare stakeholders to enrich discussion and comprehension. Thus, the qualitative and inductive approach to research was better suited to explore an emerging social phenomenon such as PE in medicine development (Hedge, 2015; Popper, 2004).

It is worth noting that, traditionally, medicine development has a strong positivist heritage, whereas value is about the world as it ought to be, with an interpretivist epistemology calling for context-specific knowledge (Kelly et al., 2015). PE emphasizes creating patient value through the social interactions of patients with PHARMA, which suggests that the meanings of PE in medicine development are continually being accomplished by the social interactions of relevant healthcare stakeholders, thus indicating a social constructivist stance (Bryman, 2015). Moreover, these philosophical underpinnings associated with PE in medicine development resonate with my own social constructivist stance that knowledge is to be found neither inside a person, nor outside in the world, but rather in the interactions between the person and the world (Kvale & Brinkmann, 2009). Since the aim of this study was to explore the understandings and practices of the concept of PE in medicine development from a value-creation perspective, adopting the stance of social constructivism and an interpretivist paradigm with qualitative inquiries was deemed more consistent with the exploratory nature and the research objectives of this study and, therefore, was considered the most appropriate research paradigm for the present study. Based on this research paradigm, the research methods designed for the present study are further elaborated upon in the following sections.

3.3 Concept analysis and development

Over recent decades, interest in exploring concepts within the healthcare and medicine disciplines has increased, with a desire to establish conceptual clarity about new phenomena (Ayton et al., 2018; Basch, 2013; Bendapudi & Leone, 2003; Berger, Flickinger, Pfoh, Martinez & Dy, 2014; Berwick, Nolan & Whittington, 2008). This desire is associated with the recognition that well-defined concepts are prerequisite to building a scientific research base for a disciplinary domain, because concepts are the building blocks of theory construction (Bright et al., 2015; Cronin, Ryan & Coughlan, 2010).

Concept analysis examines the content and structure of abstract concepts with ambiguous meanings (Walker & Avant, 2011) and various approaches exist, with overlapping aspects based on different philosophical foundations (Rodgers, 1989). Wilson (1963, pp. 23–24) introduced an original concept analysis model which includes eleven linear steps, 'isolating questions of concept, finding right answers, model cases, contrary cases, related cases, borderline cases, invented cases, social context, underlying anxiety, practical results, and results in language'. Despite the strength of this method in defining the core characteristics of a concept through a simple and achievable procedure, it was criticized due to its reductionist and deductive essentialist approach, which overlooks other contextual factors such as historical and cultural influences (Beckwith, Dickinson & Kendall, 2008a; Hupcey, Morse, Lenz & Tason, 1996). Walker and Avant (2011) adapted Wilson's method by introducing the new steps of defining attributes, antecedents, consequences, and empirical referents, thus providing context to support understandings of the concept of interest. Furthermore, an iterative concept-analysis approach, based on eight steps, was proposed by Walker and Avant (2011, pp. 160–168), 'select a concept; determine the aims or purposes of analysis; identify uses of the concept; determine the defining attributes; identify model case(s); identify additional cases; identify antecedents and consequences; and define

empirical referents'. Although this approach has advanced the theoretical development of a concept by providing more precise analysis and context, it has the limitation of lacking scholarly rigour in literature review strategy and critical appraisal; moreover, it follows a deductive and reductionist approach and lacks in-depth interpretation (Lebel, Alderson & Aita, 2014). Thus, the concept-analysis approaches from both Wilson (1963) and Walker and Avant (2011) follow a deductive positivist paradigm based on an essentialist position, i.e. the attributes fundamental to the essence of a concept are thought to exist independent of context and unaffected by change and motion in the world (Rodgers & Knafl, 2000). Furthermore, these two concept-analysis approaches are based on a strong positivist epistemological view of concept as an entity, and do not offer the capability to explore a complex social phenomenon, such as PE in medicine development, within a multi-faceted contextual environment which is continually changing over time. The concept analysis approaches from both Wilson (1963) and Walker and Avant (2011) were, therefore, rejected by the present study.

A hybrid approach to concept development was suggested by Schwartz-Barcott and Kim (1986) which covers three phases – theoretical, fieldwork and final analysis – to identify, analyse and refine concepts. This hybrid approach was considered useful in integrating meanings of concepts by corroborating findings from both the literature and the empirical observations with an inductive qualitative approach (Chang, Oh, Park, Kim, & Kil, 2011; Darch, 2016). However, the methodology does not include the identification of attributes, antecedents, consequences and empirical referents, and is therefore considered to lack contextual considerations of concept development (Rodgers & Knafl, 2000). The hybrid approach from Schwartz-Barcott and Kim (1986) was thus rejected by the present study, because it was not considered an appropriate method for studying a highly context-

dependent social phenomenon, such as PE in medicine development from a value-creation perspective, to address the research objectives.

Rodgers (1989) offered an advanced concept development methodology based on an evolutionary view of the concept-development lifecycle. This view suggests that concepts evolve and serve some pragmatic utility, rather than being static or having an inherent truth. Three distinct aspects of concept development advocated by Rodgers (1989) are (i) significance (concepts acquire meaning through serving a relevant purpose, such as resolving problems or characterizing phenomena); (ii) use (the common manner of employing the concept, including means of expression and attributes of the concept); and (iii) application (applying the concept in new situations for evaluation and refinement). The notion of evolutionary concept development emphasizes conceptual change and refinement 'to maintain a useful, applicable and effective concept' (Rodgers & Knafl, 2000, p. 81). The present study focuses on exploring the (i) significance and (ii) use aspects of the concept of PE in medicine development from a value-creation perspective, which is directed towards clarification of the concept and its current use as a basis for further concept development.

The principal criticisms of the concept-analysis approaches discussed above are (i) the uncritical use of these frameworks without cautious scrutiny of their ontological and epistemological basis (Beckwith, Dickinson & Kendall, 2008b); (ii) the lack of an adequate justification of the defining attributes of a concept (Beecher et al., 2017); and (iii) the lack of scientific rigour in data selection and analysis (Penrod & Hupcey, 2004). However, these potential methodological issues can be resolved through an in-depth discussion of the link between the chosen concept-development approach and its underlying philosophical and theoretical perspectives, to show consistency and coherence, thus justifying the chosen concept-development methodology and demonstrating scientific rigour (Beecher et al., 2017; Penrod & Hupcey, 2004).

In the present study, Rodgers' (1989) evolutionary concept development approach was chosen as the methodological framework to explore the concept of PE in medicine development from a value-creation perspective, and this was discussed and justified in relation to the research questions and research paradigm adopted for the present study (see Section 3.4). A remarkable number of studies in the context of healthcare and medicines have successfully applied Rodgers' (1989) evolutionary approach in concept development, including studies on surviving cancer (Doyle, 2008) and health-seeking behaviour (Poortaghi et al., 2015). Moreover, Rodgers' (1989) approach has been demonstrated as a valid method for developing knowledge in nursing science (Tofthagen & Fagerstrom, 2010). Lastly, Rodgers' (1989) emphasis on continuity in concept development and the relevance of context to a concept align with my interpretivist epistemology and social constructivist stance (as described in Section 3.2) and was therefore adopted to address the research objectives in the present study (see Section 1.2). The research methodology framework for the present study, based on Rodgers' (1989) evolutionary concept development approach, is discussed further in the next section.

3.4 Research methodology framework

Given the research objectives of this study (see Section 1.2) and the researcher's philosophical paradigm based on interpretivism and social constructivism (see Section 3.2), Rodgers' (1989) evolutionary concept-development approach was chosen as the methodological framework for the present study to explore the concept of PE in medicine development from a value-creation perspective. This approach informed the research activities, data collection and analysis in the present study to address the research objectives (see ***Table 5***). Detailed discussion and justification of the chosen research methodology framework, in relation to the research objectives, research paradigm and theoretical perspectives adopted for the present study, are provided in Sections 3.5 and 3.6.

Table 5: Research methodological framework in the present study based on Rodgers' (1989) approach

Research Objectives (ROs)	Research Activities	Data Collection & Analysis
RO1: To explore current understandings of the concept of PE in the context of medicine development from a value-creation perspective.	**Theoretical Phase (Chapter 4):** • Identify the concept of interest and associated expressions. • Identify and select an appropriate realm (setting and sample) for data collection. • Data collection and analysis to identify the antecedents, attributes, consequences, barriers, facilitators of the concept of PE in medicine development from a value-creation perspective. • Identify surrogate terms and related concepts. • Explore empirical examples of the concept of PE in the context of medicine development • Develop a thematic map based on literature analysis about PE in medicine development from a value-creation perspective.	Database search: • SCOPUS • PubMed • EMBASE • Web of science Publications 2012–2019 in: • Research & Development • Health Authority Regulations • Health Technology Assessment • Healthcare Services Data Analysis Method: • Thematic Analysis
RO2: To explore practices and perceptions regarding the concept of PE in the context of medicine development from the perspectives of key stakeholders from a value-creation perspective.	**Fieldwork Phase (Chapter 5):** • Gather empirical data to expand the PE concept development concerning antecedents, attributes, consequences, facilitators, and barriers in the context of medicine development. • Develop a thematic map based on empirical experiences to explore practical understandings of PE in medicine development from a value-creation perspective based on interviews.	Data Collection Method: • Purposive sampling • Semi-structured interviews • Inductive qualitative inquiry • Interviewees (N=32) Data Analysis Method: • Thematic Analysis
RO3: To develop a PE conceptual framework and theoretical propositions in the context of medicine development from a value-creation perspective, informed by the above understandings.	**Final Analytical Phase (Chapter 6):** • Develop a final thematic map about PE in medicine development through corroborating empirical findings from fieldwork with theoretical data from a value-creation perspective. • Develop a final PE definition in the context of medicine development from a value-creation perspective. • Develop a PE conceptual framework and theoretical propositions in medicine development from a value-creation perspective	Data Analysis Method: • Data Triangulation

Drawing upon the discussion from previous chapters, PE in medicine development is seen as an emerging social phenomenon lacking theoretical development; therefore, an in-depth understanding of *what* and *how* questions relating to PE in medicine development from a value-creation perspective was deemed necessary to advance the knowledge (Domecq et al., 2014; Higgins et al., 2017). Based on the above recommendations, the present study aims to address these research issues through qualitative inquiries of the literature and relevant stakeholders to generate a holistic understanding of this concept inductively, based on insight and data (see Section 1.2). Furthermore, the value-creation perspective based on VBM, VCC and SDL theories, adopted in the present study, suggests the existence of multiple realities concerning PE in medicine development, which are associated with an interpretivist

ontological worldview, with an emphasis on understanding and interpreting of a concept (Hegde, 2015). Following this world-view, different people construct meanings differently, even in relation to the same phenomenon, because socio-cultural, contextual factors can significantly influence the construction of concepts (Crotty, 1998). Therefore, in the present study, understandings about PE in medicine development are consciously explored from the perspectives of different stakeholders (patients, medicine developers and PE experts) to create a holistic account of this PE phenomenon, which is based on the researcher's social constructivist understanding of knowledge as socially constructed and inherently context-bound (Bryman, 2016). Similarly, Rodgers' (1989) concept-development approach emphasizes context-dependant inductive, qualitative, interpretivist enquiry, developing the concept by capturing perspectives from real-world practitioners who have first-hand experience. It thus resonates with the research questions, research paradigm, and theoretical perspectives adopted in the present study and is therefore deemed as most appropriate to explore the phenomenon of PE in medicine development and address the research objectives in the present study.

The importance of specifying theoretical perspectives to guide qualitative research design was argued by Lewis and Ritchie (2003): the generalization of qualitative findings requires application from a clearly defined theoretical perspective, which should support the consistent use of multiple methods for data collection, to enhance the reliability of data analysis and, thus, the coherence of the study. These principles are consistently followed in the present study, through the application of a defined value-creation theoretical perspective (based on VBM, VCC, and SDL) serving as an analytical lens to explore the PE phenomenon in medicine development (as discussed in Section 2.5). This theoretical perspective has informed the design of data collection (such as the devise of interview questions), analysis and interpretation of the study findings, to ensure focus, consistency, and coherence

throughout the study. In addressing the research objectives of this study, a methodological framework based on Rodgers' (1989) evolutionary concept development approach was considered appropriate and justified.

According to this methodology framework (see ***Table 5***), the study was conducted in three phases: (i) theoretical phase, (ii) fieldwork phase and (iii) final analytical phase. In the theoretical phase, a thematic analysis of the literature (as data) was conducted to establish a baseline understanding of the concept of PE in medicine development from a value-creation perspective, aiming to address the first research objective (RO1 - to explore current understandings of the concept of PE in the context of medicine development from a value-creation perspective). Following Rodgers' (1989) concept-development approach, to address RO1, a multi-disciplinary (including medicine research and development, health authority regulations, health technology assessment and healthcare services, covering the whole lifecycle of medicine development processes) systematic search of the literature published between 2012 and 2019 was conducted on the concept of PE in medicine development. Literature was reviewed, appraised, and selected according to its relevance to the concept of PE in medicine development. Coding and thematic analysis (with the aid of NVivo software) were applied to the selected data to develop a provisional thematic map regarding the antecedents, attributes, consequences, facilitators, barriers and exemplars to the concept of PE in medicine development from a value-creation perspective. This formed the exploration of the concept of PE in medicine development, based on a thematic analysis of the current literature to address RO1 of the present study (see also Section 1.2).

Following the literature-based, theoretical concept analysis, Rodgers (1989) suggested an expanded concept development using practical evaluations, especially with those involved in real-life settings, to extend the concept development with practical meaning. Interviews are considered a powerful method to explore the perspectives and

experiences of different practitioners. Therefore, this expanded concept development method was adopted in the present research to address RO2 (i.e., to explore practices and perceptions regarding the concept of PE in medicine development from the perspectives of key stakeholders from a value-creation perspective). For exploring perspectives and experiences of different PE-related practitioners, focus groups could be a method where group interviews with several participants involved are conducted to discuss a certain topic (Bryman, 2016). The strength of focus group interviews lies in the collective account of what people think through arguing and challenging each other's views, while the disadvantage of this method is that some members might not express their personal honest opinions under the group dynamic (Braun & Clarke, 2013). If the participants do not feel comfortable to share their individual knowledge and experiences in the form of a group discussion, focus group interviews will not generate any useful deep insights (Creswell, 2017). The present study aims to capture in-depth practical understandings regarding PE in medicine development from each individual participant with diverse backgrounds and perspectives, focus groups interview method could not serve this purpose, therefore, was rejected by the present study. Individual interviews were considered more appropriate to serve the aim of the present study and thus adopted as data collection method for the fieldwork.

Interviews are defined as a professional conversation aimed at capturing the experiences and perspectives of the participants in relation to a topic of interest (Kvale & Brinkmann, 2009). They are categorised as structured, semi-structured and unstructured (or in-depth) (Creswell, 2017). Semi-structured interviews are primarily used to capture the understandings and experiences of interviewees in qualitative inquiries; they allow participants' insights to be captured by following a set of pre-defined questions yet retain the flexibility to explore emerging topics more deeply (Kvale & Brinkmann, 2009). The semi-structured interview allows the researcher to acquire information based on a set of

open-ended, amendable questions with a flexible structure, which also allows participants to raise issues that the researcher may not have anticipated, and is the most common type of interview in qualitative research (Braun & Clarke, 2013). It is considered especially useful for theoretical research through 'eliciting data grounded in the experience of the participants as well as data guided by existing constructs in the particular discipline within which one is conducting research' (Galletta, 2013, p. 45). Since RO2 of the present study is to explore the practices and understandings of the concept of PE in medicine development from the perspectives of key stakeholders, a semi-structured interview method was considered most appropriate, as it allows an inductive conceptualization of PE based on the diverse personal experiences and deep insights of the participants.

An interview guide (see ***Annex 2***) was developed, based on the adopted theoretical perspectives (see Section 2.5) and the research questions (see Section 1.2) of the present study. For instance, the interviewees were asked to share their understandings about PE in medicine development from a value-creation perspective, and their experiences about how value can be co-created within PE in medicine development, which are linked with the guiding questions from a VCC perspective. Participants for semi-structured interviews were recruited based on the purposive sampling of PE-related key stakeholders (i.e., patients, medicine development experts and PE experts) who had relevant knowledge. Individual interviews of up to 60 minutes each were conducted with 32 participants to allow sufficient variability and data saturation for inductive theory-building (Bryman, 2015). The sample size was consistent with that proposed by Saunders and Townsed (2016) as an appropriate average number of participants for a qualitative study.

After the interviews, the data were transcribed, coded, and thematic analysis was applied to capture saturated meanings, identify themes and patterns and address the research questions (Bazeley, 2013; Creswell, 2017). The coding and thematic analysis were supported

by use of NVivo, well-established software for assisting in managing data and ideas effectively and efficiently, allowing researchers to focus on examining the meaning of what is recorded (Bazeley & Jackson, 2013). In-depth interviews with these 32 participants allowed the generation of rich and vivid accounts about PE in medicine development from the perceptions of experienced practitioners in this field, which proved adequate for both acquiring profound insight into the PE topic and allowing theoretical generalization by developing a PE-related thematic map (for further discussions, see Section 3.5.2).

Lastly, in the final analytical phase, theoretical and empirical data were corroborated and integrated following an inductive procedure of multiple data-making through triangulation (Boyatzis, 1998; Yin, 2016). Insights found from the thematic analysis of both literature and empirical data were used to inform the development of a final PE conceptual framework in medicine development from a value-creation perspective. A final definition of PE in medicine development was provided based on the insights gained in this study. The respective data collection and analysis methods used in each phase are elaborated upon in the following sections.

3.5 Data collection methods

Data collection took place in two phases: the theoretical phase and the fieldwork phase. In the theoretical phase, a systematic literature search was performed, aiming to characterize the concept of PE in medicine development and address RO1. In the fieldwork phase, semi-structured interviews with relevant key stakeholders were conducted to gather empirical data, to explore perceptions and experiences related to the concept of PE in medicine development practices and address RO2. The detailed data collection methods in different phases are discussed and justified further below.

3.5.1 Theoretical phase: Literature search and selection

A systematic literature search with the term ‘patient engagement’ in the domains of healthcare and medicine was conducted in the databases PubMed, EMBASE, SCOPUS and Web of Sciences (WOS). These databases are the most comprehensive electronic sources for scholarly publications in public health, healthcare, medicines and social sciences across multiple disciplines (UIC, 2018). The initial literature review (see Section 2.4) revealed that the development focus of PE shifted in around 2012 to the medicine development domain in response to the paradigm shift of healthcare to a service-oriented, patient-centric and value-based environment (Gallivan, Burns, Bellows & Eigenseher, 2012; Mirzaei et al., 2013; Mockford, Staniszewska, Griffiths & Herron-Marx, 2012; Moore, Titler, Kane Low, Dalton & Sampselle, 2015; Roman & Feingold, 2014; Shippee et al., 2015). Literature from 2012 onwards was, therefore, considered more appropriate and selected to capture the most advanced knowledge on PE in medicine development from a value-creation perspective (Boudes et al., 2018; Danis & Solomon, 2013; Kohler et al., 2017; Lemke & Harris-Wai, 2015; Tapp, Derkowski, Calvert, Welch & Spencer, 2017). Publications in the English language from January 2012 to December 2019 were searched using the combined search terms ‘patient engagement’ and ‘medicine development’ in these databases. The search strategy revealed 278 articles in total. Following an abstract review and the removal of duplicates, 177 publications were considered relevant, retrieved from the database, and stored in EndNote software for full-text appraisal. The relevance of these articles was judged based on the review of their abstracts: articles were judged to be relevant if the abstract indicates a relationship to the research topic, or the research questions, or the initial theoretical perspectives (based on VBM, VCC, and SDL). The evolutionary approach developed by Rodgers (1989) suggests including at least 30 articles from each discipline or 20% of the literature deriving from each discipline in the literature review. However, this

sampling approach has been criticized as it can cause the omission of important citations (Beckwith et al., 2008a; Hupcey & Penrod, 2005). Thus, in the present study, full-text reviews of all 177 relevant publications were conducted, considering the following eligibility criteria: (i) articles presenting definitional elements of the concept of interest (such as patient centricity, patient value, patients as consumers and experts, patients as value co-creators), or (ii) scholarly articles presenting theoretical discussions of the concept of interest, or (iii) studies exploring the meanings or empirical findings of the concept of interest. A critical appraisal of the sampled literature based on pre-defined eligibility criteria helped the researcher to focus on the articles most relevant to the research questions, to provide high-quality data for reliable research to support or refute claims (CASP, 2018). After the assessment of eligibility, 156 final articles (uploaded and stored in NVivo) were included in the thematic analysis of data from the literature to explore contemporary understandings about PE in medicine development. The final shortlist of 156 selected articles originated mainly from North America (i.e., USA and Canada), Europe and the UK. The prevalence of the PE literature in these western countries is likely influenced by PE-related political factors (e.g. democratization of health information, empowerment of patients as consumers) (Accenture, 2014; Blasimme & Vayena, 2016), economic factors (e.g. healthcare sustainability issues to balance innovation and cost containment) (Crawford et al., 2017; Duffett, 2017), organisational factors (e.g. the emergence of patient organisations as a strong partner, the enforcement of PE by regulations) (Perfetto et al., 2015; Richard et al., 2017), and cultural factors (e.g. respecting citizen's rights with a long history of PPI in healthcare) (Beier 2019; Biddle 2020). These favourable social factors in these western countries have been playing important roles that drive the advancement of PE in medicine development, with North America, Europe and the UK being front-runners of this PE movement, as

reflected in the prevailing PE-literature originating from these regions (NICE, 2015; Robinson, 2013; S. K. Smith et al., 2015).

The literature search and selection for the conceptualization of PE in medicine development in the theoretical phase is depicted in ***Figure 4***. The thematic analysis of the literature data in the theoretical phase identified core themes regarding antecedents, attributes, consequences, facilitators, barriers, surrogate terms, related concepts, empirical exemplars concerning PE in medicine development following Rodgers' (1989) methodology (see ***Table 5***). These findings from the theoretical phase address the RO1 of the present study, which are presented and discussed in Chapter 4.

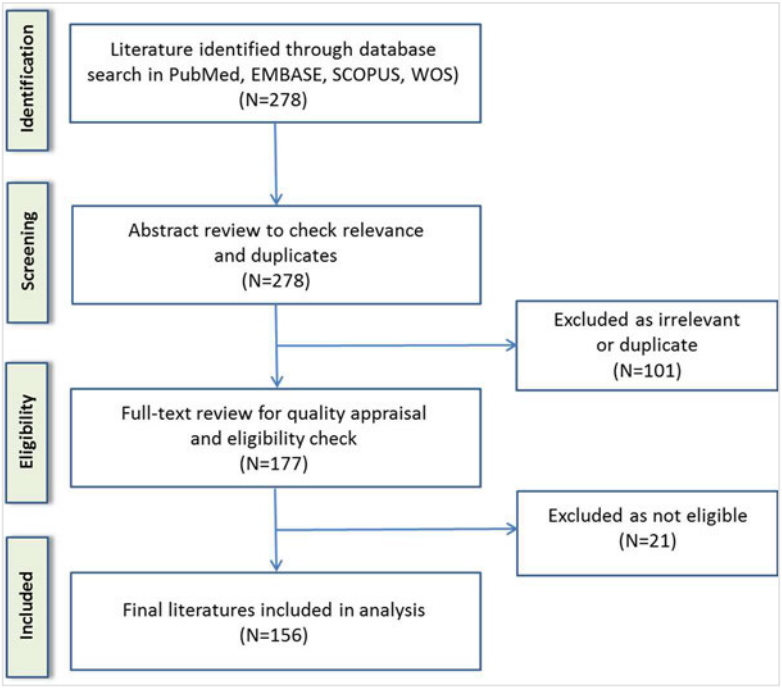

Figure 4*: Literature search and selection flow for the conceptualization of PE in the theoretical phase*

3.5.2 Fieldwork phase: Semi-structured interviews

Following the notion of an expanded concept development approach from Rodgers (1989), the literature-based concept analysis is not the final point in concept development; the utility and value of a concept must be expanded and further developed through practical insights to gather empirical meanings from real-world experience. Interviews are considered

a useful method to capture insights and explore perspectives from practitioners to understand the practical 'use' of a concept in the real world, serving as 'a means to expand and clarify the definition derived from a review of the literature' (Rodgers & Knafl, 2000, p. 323).

An interview guide (see ***Annex 2***) was developed, based on the RQs (see Section 1.2) and the initial theoretical perspectives based on VBM, VCC, and SDL (see Section 2.5), and was applied consistently to comprehend the PE phenomenon from diverse perspectives while allowing an inductive theoretical generalization grounded in data. Interview participants were recruited based on purposive sampling; key stakeholders (i.e., patients, medicine development experts and PE experts) with relevant knowledge were sought for the semi-structured interviews. Purposive sampling is a deliberate, non-random sampling method aiming to capture experience and knowledge from participants with particular characteristics (Bowling, 2014). The selection of the sampling method needs to consider the following factors: (i) the relevance to the research questions; (ii) the theoretical perspective of the research, (iii) the data analysis method and saturation point and (iv) the heterogeneity of the population and the minimum requirements for an adequate sample (Bryman, 2015). In the present study, a purposive sampling method was considered most appropriate to explore the emerging PE phenomenon among stakeholders who have particular experiences and knowledge within this domain (Kvale & Brinkmann, 2009). The data obtained from the semi-structured interviews were used to comprehend the meanings and core themes regarding the concept of PE in medicine development from empirical perspectives and to generate new insights. In this regard, an inductive qualitative thematic analysis method was applied to analyse the interview data. A minimum of 30 interviewees was planned to include a diversity of relevant stakeholders, including groups of (i) patients (who have experience in participating in medicine development), (ii) medicine development experts (who work in the pharmaceutical industry) and (iii) PE experts (who are PE advocates or leaders in PE

thinking, either from patient organisations or other PE initiatives). A minimum of 30 interviewees was suggested as appropriate for a qualitative study considering both credibility and data saturation (Adler & Adler, 2012; Warren, 2002). Nevertheless, following data saturation principles and aiming for an inductive conceptualization of PE in medicine development, the interview sample size was not fixed, but remained flexible and was guided by the need to achieve an inductive data saturation point for theory-building in the final analytical phase. Data saturation is reached when no new information or themes are added by new interviewees and the identified themes become stabilized (Bryman, 2015).

A pre-defined recruitment strategy for the interviews was developed for the fieldwork phase (see ***Annex 3***). Potential interview candidates were sourced through pharmaceutical industry association websites (e.g., the leading European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Pharmaceutical Research and Manufacturers of America (PhRMA)), social media sites and websites of patient organisations, and websites of leading patient engagement initiatives in the EU and the USA. Moreover, the researcher's professional networks and relevant conferences were used to recruit PE experts with relevant knowledge and experience. Potential candidates were invited by email (see ***Annex 4***) to express their interest in participation. After indicating such interest, the participant information sheet (see ***Annex 5***) covering the purpose and nature of the research, data protection measures and privacy notices, together with the informed consent form (see ***Annex 6***) were shared. Written informed consent was obtained from each potential participant prior to interview, after receipt of which, the researcher scheduled an interview with the potential participant.

Face-to-face interviews, conducted in a natural and safe environment, were preferred to catch both verbal and nonverbal language (Galletta, 2013). Interview locations were therefore chosen to be non-threatening, relaxed, and allowing confidentiality, enabling the

interviewee to think, remember and talk freely. The participant was asked to choose a place where they felt comfortable, for example, their home or a quiet cafeteria, so that the researcher's influence was as minimal as possible. If distance prevented face-to-face interviews, Skype interviews were conducted. Skype interviews have been reported to be an effective interview method, very similar to an in-person interview, since the visual element allows interview partners to see each other, akin to a face-to-face interview (Deakin & Wakefield, 2014; Weinmann, Thomas, Brilmayer, Heinrich & Radon, 2012). If neither of the above options were possible, interviews were conducted by telephone. The data generated from the conversations remained anonymous at all times, treated as strictly confidential and used only for the purposes of the present study, following the EU General Data Protection Regulations (GDPR, 2018). Furthermore, the present study obtained ethical approval from the University of Gloucestershire Research Ethics Committee in 2018 (see ***Annex 7***) prior to the study being conducted to ensure ethical compliance.

Interview data gathered in qualitative studies are used to obtain in-depth insight into social phenomena, in contrast to the representative quality assumed by probability sampling in quantitative research (Bowling, 2014). The sample size in qualitative interviews should be large enough to achieve data saturation, but not too large to allow an in-depth analysis of the interview cases (Onwuegbuzie & Leech, 2010). Following these principles, individual interviews with 32 participants in the present study allowed sufficient variability and data saturation for inductive theory-building (Galletta, 2013). The interview participant profiles in the fieldwork are presented in the next section.

3.5.3 Interview participant profiles

A purposive sampling method was employed, aiming to recruit diverse stakeholders who were willing to share their understandings and experiences of PE in medicine

development (see discussions in Section 3.5.2). Interview candidates were recruited according to pre-defined recruitment strategy (see ***Annex 3***).

As a result, 32 interviewees, including patients and patient advocates (*n*=11), medicine developers from PHARMA companies (*n*=10), and PE experts from academia and public institutions (*n*=11) were recruited for a one-hour semi-structured interview. The greatest number of interviewees were based in North America (50%) while the rest were based either in Europe and the UK (40%) or Asia Pacific (10%) (see ***Table 6***). The majority of participants (90%) being from North America, the EU and the UK reflects, to some extent, the advancement of PE in these western countries as front-runners, especially considering the favourable social factors (i.e., economic, political, cultural, and organisational) that may facilitate the PE movement in medicine development (see discussions in Section 1.1 and Section 3.5.1). Nevertheless, the balanced participants from patients, PHARMA, academia, and public associations across the globe were intended to reflect their respective cultural, organisational, and social diversity that may, in turn, have shaped their understandings and perceptions of the PE phenomenon based on their roles and country of origin.

Most of the interviews were conducted via skype and/or telephone (81%) due to distance constraints, with the remaining 19% conducted face-to-face at a location chosen by the interviewees. Interviewees' perspectives were captured to identify themes concerning antecedents, attributes, consequences and influencing factors of PE in medicine development at the various levels – society, patient, and PHARMA respectively. This analysis aims to provide a comprehensive account of the PE phenomenon, grounded in the rich narratives offered by the study participants. Roughly the same number of participants from each of the PE stakeholder groups was achieved to capture a broad range of insights and balance diversity in each stakeholder group. Participant demographics regarding gender, age ranges and country of origin are presented in ***Table 6***.

Table 6: Interview participant profiles in the fieldwork

Patients and Patient Advocates (PT) (Patient's perspective)				Medicine Developers (MD) (PHARMA's perspective)				PE Experts (PX) (Societal perspective)			
Participant	Country	Gender	Age	Participant	Country	Gender	Age	Participant	Country	Gender	Age
P-03 (PT)	DE	F	30s	P-01 (MD)	ES	M	50s	P-02 (PX)	US	M	30s
P-07 (PT)	UK	M	60s	P-08 (MD)	DE	F	30s	P-04 (PX)	US	F	50s
P-09 (PT)	CA	F	60s	P-13 (MD)	CH	M	30s	P-05 (PX)	US	F	30s
P-10 (PT)	US	F	40s	P-15 (MD)	DE	F	40s	P-06 (PX)	US	M	60s
P-12 (PT)	US	F	40s	P-19 (MD)	DE	F	50s	P-11 (PX)	AU	F	40s
P-14 (PT)	US	F	40s	P-20 (MD)	PL	F	40s	P-16 (PX)	NL	M	60s
P-17 (PT)	US	F	60s	P-21 (MD)	CN	F	40s	P-18 (PX)	US	F	60s
P-25 (PT)	US	F	50s	P-22 (MD)	CN	M	40s	P-23 (PX)	UK	M	50s
P-26 (PT)	US	F	50s	P-27 (MD)	UK	M	50s	P-24 (PX)	NL	F	30s
P-29 (PT)	US	F	50s	P-30 (MD)	US	M	50s	P-28 (PX)	US	F	40s
P-31 (PT)	US	F	50s					P-32 (PX)	BE	F	50s
n=11				*n*=10				*n*=11			

P: Participant; n: number of participants; PT: Patient; MD: Medicine Developer; PX: PE Expert; M: Male; F: Female; 30s – 60s: age range
DE: Germany; UK: United Kingdom; CA: Canada; US: United States; ES: Spain; CH: Switzerland; PL: Poland; CN: China; AU: Australia
NL: Netherland; BE: Belgium

The recruitment and interview schedules ran in parallel to the data analysis and continued until saturation point (i.e., until no new themes emerged from the interviews through the inductive thematic analysis), and the emerging core themes became saturated and stabilized (Richards, 2015). Thus, the researcher was able to spot any shortcomings in the early data collection processes and had the opportunity to improve the data collection techniques in the next interviews (Braun & Clarke, 2013). Furthermore, through parallel data analysis processes, the researcher made continuous checks for unanticipated themes or ideas to see whether additional data was needed to address the research objectives for the final analysis (Boyatzis, 1998).

The interview guide covered thirteen open questions, prompting areas to be covered related to the concept of PE in medicine development. Although the focus of the interviews was thematizing the stakeholders' understandings of the concept of PE in medicine development – i.e., the *what* and *how* question about PE in medicine development from a value-creation perspective, spaces were given for participants to explain *why,* regarding their constructed meanings about PE in medicine development, which offered rich contextual information and in-depth insight into the PE phenomenon in real-life situations.

All interviews were conducted in English and audio recorded. Verbatim transcription was performed promptly by the researcher after each interview and stored in the NVivo

software for further data analysis. The records were read and re-read to enable the researcher to become immersed in and familiar with the data. The transcriptions were then coded by the researcher following an inductive, qualitative coding approach, guided by the research questions (see Section 1.2) and the initial theoretical perspectives based on VBM, VCC, and SDL (see Section 2.5). In contrast to quantitative coding, with data reduction as a focus, qualitative coding is about data retention, learning from the data and organizing it to generate categories, understand patterns and develop insights about the topic of interest (Richards, 2014; Saldaña, 2016). Following these considerations, the interview data were quoted line by line with an open coding approach to identify categories and themes derived from the codes; based on which, the themes were then organized according to the key aspects of PE in medicine development (i.e., antecedents, attributes, consequences, barriers and facilitators as defined in the methodology framework of the present study - see ***Table 5***) to generate a provisional thematic map. These identified themes represent the contemporary practical understandings regarding PE in medicine development from PE-related practitioners and address the RO2 in the present study (see Section 1.2).

NVivo proved to be helpful in supporting the inductive qualitative coding and data analysis processes in the present study. Early critics of the use of software-based coding argued that the researcher may lose their closeness to the data, thus making analysis more mechanical and more akin to a quantitative approach (Bazeley, 2013). However, modern software such as NVivo was designed to allow researchers to remain sufficiently close to the data for familiarity, while having sufficient distance for abstraction, thus contributing to sophisticated qualitative data analysis with efficiency, transparency and rigour in its processes (Bazeley & Jackson, 2013; Richards, 2014). In the context of the present study, a huge dataset (i.e., 211 sources with 1,673 references derived from the interview analysis, and 690 sources with 3,058 references derived from literature analysis) was generated and

stored in NVivo as an evidence base and audit trail to support the thematic maps developed and their relationship with the collated raw data. It would be not possible to generate themes based on this amount of data through a manual coding process. Consequently, thematic analysis and multiple data-making via data triangulation with the support of NVivo were chosen as methods for data analysis and interpretation in the present study, as discussed further in the following sections.

3.6 Data analysis and interpretation

Data analysis is the management, analysis, and interpretation of the data. It aims to make sense of the data to obtain insights and to understand the research phenomena (Bryman, 2015). There are many different qualitative data-analysis methods; the selection of an appropriate method needs to be aligned with the research paradigm, the theoretical perspective, and the research methodological framework, and is guided by the research questions of a study (Braun & Clarke, 2013).

Thematic analysis (TA) is a method widely used in qualitative research to identify, analyse, organize, describe, and report themes found within the data. It can offer a rich and complex account of the data and to generate trustworthy and insightful findings (Braun & Clarke, 2013). TA was chosen as the primary qualitative data-analysis method in the present study for both the theoretical and fieldwork analysis due to its broad deployment compatibility in different contexts (Bryman, 2015). Furthermore, in the final analytical phase, data triangulation was used to examine the evidence gathered from different sources (literature and interviews) to build an integrated evidence base and offer a coherent justification for the final study results (Creswell, 2017). The data analysis and interpretation methods used in this study are discussed and justified in detail in the next sections.

3.6.1 Thematic analysis

Thematic analysis (TA) is a data analysis method commonly used in qualitative studies in healthcare research and social sciences (Bowling, 2014; Bryman, 2015). It was first developed by Gerald Holton in the 1970s and was further developed as a distinctive method for a broad spectrum of qualitative research at the beginning of the twenty-first century with a clear set of procedures for the social sciences (Braun & Clarke, 2013). TA is defined as 'a method for identifying themes and patterns of meaning across a dataset in relation to a research question; possibly the most widely used qualitative method of data analysis' (Braun & Clarke, 2013, p. 175). It covers familiarization with the raw data, developing thinking about the data via coding, elaborating categories based on codes, evaluating themes and patterns and writing up insights (Bryman, 2015). Reading and becoming acquainted with the data (transcripts, memos documents, etc.) is a crucial first step before coding. Coding assigns a summative, salient, evocative attribute to a chunk of data and is a researcher-generated construct serving as a critical link between the data and ideas (Saldaña, 2016). Codes are repeatedly revisited and subsequently categorized for pattern-detection and theory-building (Charmaz, 2006).

Bryman (2015) emphasized the importance of maintaining an audit trail of key decisions concerning coding, the identification of themes and evidence-based conceptualization to justify how the themes were developed. Following this recommendation, the TA process employed in this study is described in greater detail here for the sake of transparency. A variety of coding approaches (inductive, theoretical, experiential, constructionist, etc.) exist, with different ways of identifying themes (Braun & Clarke, 2013). In the theoretical phase of the present study, an inductive coding approach was applied for an initial analysis of PE from the literature data of 156 selected articles (for the literature search and selection process, see ***Figure 4***). An inductive TA aims to generate insight

bottom-up from the data, without being overly influenced by existing theory, although 'analysis is always shaped to some extent by the researcher's standpoint, disciplinary knowledge and epistemology' (Braun & Clarke, 2013, p.175). The initial TA of the literature data informed the development of a provisional thematic map of PE in medicine development from a value-creation perspective based on VBM, VCC and SDL (see ***Figure 8***), which revealed the underlying theoretical cores of PE in medicine development. In the fieldwork phase, an inductive TA coding approach was again applied to the interview data, leading to the development of a second thematic map of PE in medicine development from a value-creation perspective (see ***Figure 9***). Throughout the inductive TA processes in the present study, the defined methodological framework (see ***Table 5***) offers a structure within which to organize the codes and categories across all aspects of PE in medicine development (i.e., antecedents, attributes, consequences, barriers, facilitators, etc.) at the patient, society, and PHARMA levels. The initial theoretical perspectives (see Section 2.5) serve, thus, as a lens to interrogate the data in searching for answers to *what* and *how* questions regarding PE in medicine development throughout the inductive coding and TA processes.

There are three steps in developing codes and themes from an inductive data-driven TA approach: (i) generate the code (the initial description terms are informed by the literature if there is a definition for the construct); (ii) review and revisit the code repeatedly in the context of the raw data to generate themes (determine the compatibility of the provisional themes with the raw data and, possibly, refine the themes to ensure applicability); and (iii) determine the reliability of the coders and the codes to ensure consistency of judgement (Boyatzis, 1998). Following this approach, within the inductive data-driven TA processes in the present study, firstly, codes were generated through a line-by-line analysis of the raw data. The descriptions of these codes were generated through the researcher's interpretation and documented in analytical memos. Next, further analysis of these preliminary codes was

performed by comparing similarity and overlap among the meanings of the codes. Through these processes, broader categories were identified which captured the most salient meanings across the codes. Furthermore, a deeper analysis of the coded data, codes and categories was conducted to identify broader patterns – themes – among these data. In the present study, a theme is defined as a central organising concept that captures the salient meanings within the dataset in relation to the research questions (Braun & Clarke, 2013). Lastly, overarching core themes were developed, grounded in the identified themes and categories, to support a coherent and focused account of the data that convey the breadth and diversity of patterns to allow further theory building (Braun & Clarke, 2013). The presence of core themes allows the generation of a testable, relevant, and valid theory (Boyatzis, 1998).

Throughout the present study, the provisional themes concerning PE in medicine development were continually explored by repetitive review of the raw data and the codes developed to help the researcher to gain a sharper picture of the evidence, to refine the thematic map and to minimize researcher bias by listening to the data (Boyatzis, 1998). To further enhance the consistency and transparency of the coding and inductive TA analysis grounded in data, coding books were developed to make the TA processes explicit and help the reader understand how the researcher made sense of the data throughout this process. The coding books from the theoretical and fieldwork phases (see ***Annex 8*** and ***Annex 9***) compile codes, categories, themes, cross-references, and document the coding processes for the sake of transparency and enhanced validity (Richards, 2014).

Next, to increase the reliability of the coding and thematic analysis, discussions with colleagues not involved in the study were undertaken regularly throughout this process. In the case of ambiguity in codes and themes, analytical memos were revisited and discussed with these colleagues to sharpen the ideas and descriptions associated with these codes and themes. Through these processes, the researcher reflected on interpretations to ensure that

the themes were linked with the data and not imposed by the researcher. These processes were considered effective in minimizing ambiguity in the coding and reducing potential bias from the researcher (Braun & Clarke, 2013).

Bazeley (2013) observed that researchers who use TA in qualitative data analysis are often vague about how themes are identified or emerge from the data. TA is perceived by some researchers as having limited interpretative power if not used within a defined analytic framework (Braun & Clarke, 2013). Taking these concerns into consideration, it is important to justify the relevance and significance of the themes identified from the TA in relation to the value-creation theoretical perspectives (see Section 2.5) by showing how these themes relate to each other and to the other concepts, what the implications are and how they relate to other literature findings. These major research activities were undertaken in the final analytical phase of further data interpretation and theory-building in the present study to address the RO3 (findings are presented in Chapter 6). In the final analytical phase, triangulation of the data from the literature and the empirical interviews was performed to further strengthen the evidence base and enhance the validity and credibility of the research claims, as further discussed and justified in detail in the next section.

3.6.2 Triangulation

Triangulation is defined as 'the use of more than one method or source of data in the study of a social phenomenon so that findings may be cross-checked' (Bryman, 2015, p. 697). It was originally developed by Webb et al. (1966) who employed more than one method in the development of concept measures, to achieve greater confidence in the findings. The use of triangulation in qualitative studies was first promoted in sociological research by Denzin (1970) and has been further developed and used by Lincoln and Guba (1985) to capture multiple perspectives of a research phenomenon in a wide range of qualitative studies. In social sciences, triangulation has become an approach widely used by

qualitative scholars to strengthen analytical claims by interrogating data from different sources and multiple perspectives, which allows a richer, deeper and more comprehensive account of the research issues under investigation (Braun & Clarke, 2013; Silverman, 1993; J. A. Smith, 1996).

In the present study, to form a comprehensive account of the concept of PE in the context of medicine development, both the theoretical data from the current literature and the empirical data from the interviews were used in the final integrated analysis and interpretation. Moreover, in the interview phase, perspectives from different stakeholders (patients, medicine development experts, and PE experts) were captured and analysed. Thus, triangulation of data from different data sources and different perspectives was employed in the present study to enhance validity (Guion, 2002; Heale & Forbes, 2013; Silverman, 1993). In the final analysis phase of the present study, the multiple perspectives gathered from different data sources were triangulated and integrated to create a more comprehensive, reliable, and meaningful account of the concept of PE in medicine development. In so doing, the thematic maps developed from the theoretical and fieldwork phases were revisited, compared, and corroborated to develop a final conceptual framework for PE in medicine development from a value-creation perspective (see Section 6.3).

3.7 Trustworthiness of qualitative research

Criteria have been defined to assess the quality of qualitative research in terms of trustworthiness and authenticity (Lincoln & Guba, 1985). Trustworthiness considers aspects of credibility (how believable the findings are), transferability (whether the findings are applicable to other contexts), dependability (whether the findings are always applicable) and confirmability (whether the researcher has allowed their values to intrude) (Bryman, 2015; Lincoln & Guba, 1985). Authenticity concerns the wider political impact of the research outcomes, but has to date not been influential in social research (Bryman, 2015). Drawing

on factors related to trustworthiness, several checklist-based frameworks for assessing the quality of qualitative research have been developed by scholars (Elliott, Fischer & Rennie, 1999; Spencer, Ritchie, Lewis & Dillon, 2003; Tracy, 2010; Yardley, 2000). In particular, a specific quality appraisal framework for good TA in qualitative research was provided by Braun and Clarke (2013) to guide the processes of transcription, coding, analysis, interpretation and write-up. Taking these quality criteria into account, several measures were implemented in the present study to increase its trustworthiness, as discussed, and justified further in the next paragraphs.

Firstly, credibility is concerned with the internal validity of a study, that is, the degree to which what is observed is what is supposed to be observed, to come closer to the true reality of the phenomenon investigated (Mays & Pope, 2000; Robson, 2002). Coming from a social constructivist ontological stance, I did not assume a single truth but, rather, viewed meanings as multi-faceted and fundamentally bonded to the context of use. Therefore, the different data sources were triangulated, and multiple perspectives of stakeholders captured, allowing me to create a broad and deep account of PE in medicine development, thus increasing the internal validity and credibility of the final claims in the present study.

Secondly, transferability refers to the external validity of research, in parallel with the quality criteria of a quantitative study, however with different meanings (Creswell, 2017). Qualitative findings tend to be tied to the specific context and significance of the social aspects being studied; therefore, qualitative researchers are encouraged to provide a rich and detailed description of the context to convey the findings, with multiple perspectives on a theme (Lincoln & Guba, 1985). This process may convey a shared experience to the reader and help others to judge the potential transferability to other contexts (Bryman, 2015). In the present study, in-depth analysis and account of the changing healthcare and medicine development environment were offered to provide a rich description of the context which

surrounds and frames the PE phenomenon (as discussed in Sections 2.3 and 2.4). A thorough description of the contextual factors surrounding PE may provide a rich account of the social significance of the research topic and facilitate a common understanding with readers regarding the investigated phenomenon, thus enhancing the transferability of the research findings.

Thirdly, dependability relates to the reliability of a qualitative study, addressing whether the research findings are likely to apply at other times and indicating whether the researcher's approach and findings apply consistently across different projects (Bryman, 2015). The reliability of the present study was enhanced by maintaining a rigorous audit trail and offering complete transparency throughout the research processes (i.e., development of the research proposal, selection of the research methodology and design, interview transcription, data coding, analysis and interpretation). Furthermore, the research procedures and findings were discussed and challenged with two academic supervisors on a regular basis throughout the research period which served as a peer review to ensure data transparency, thus further enhancing the reliability of the research.

Lastly, confirmability is concerned with whether the researcher has imposed their personal values and theoretical assumptions on the research, although complete objectivity is not possible in qualitative research (Bryman, 2015; Kvale & Brinkmann, 2009). Researchers should maintain a constantly reflective stance, remaining sensitive to the implications of their own values, theoretical assumptions, chosen methods and epistemological backgrounds in the formation of research knowledge (Boyatzis, 1998). Further, the reflections of the researcher should be as explicit and transparent as possible, to minimize researcher bias (Braun & Clarke, 2013). Thus, the researcher takes an outside observer role as an instrument of the research, to extract knowledge through inquiry and conversation with others and then transmit it in the form of a text to readers (Bryman, 2015;

Richards, 2014). By keeping constant reflectivity and neutrality in the present study, I explored and interpreted the PE phenomenon from the perspectives of the stakeholders and the data gathered, which prompted a deeper understanding beneath the surface and generated fresh insight. The emphasis on and practice of an outsider role in the present study was consistent with the interpretivist worldview and social constructivist ontological stance I adopted for the present study. Wherever possible, I established the meanings of the research phenomena from the perspectives of the participants and data. I restricted the influence of my values and experiences to a minimum by taking a constant, reflexive stance and maintaining neutrality and transparency throughout the research, thus enhancing the trustworthiness of the present study.

3.8 Ethical consideration

The present study was conducted in accordance with the research ethics handbook of the University of Gloucestershire (UOG, 2018). Interview participation was voluntary, and participants were informed of the purpose of the interviews and their right to withdraw at any time prior to the publication. Informed consent in written form was obtained from each participant before the interview was conducted. The content of the conversations was anonymized, treated as strictly confidential and used only for the purpose of this study, following the EU General Data Protection Regulations (GDPR, 2018). The research project was approved by the Research Ethics Committee of the University of Gloucestershire in 2018 before commencing the study (see ***Annex 7***).

Some interview participants (e.g., patients or service-users) may have had negative experiences of being involved in medicine development. Some medicine development experts may have felt sensitive to the research questions due to the uncertainty and complexities in the highly regulated pharmaceutical environment. Some participants may have, unsolicited, revealed or discussed personal issues during the interviews. In such

sensitive situations, I was aware of the power asymmetry and the need to respect the privacy, dignity and well-being of the participants, and endeavoured to balance the integrity of this scientific inquiry with respect for the participants, showing empathy and sympathy to support the interviewees (e.g., by signposting to interviewees showing understandings, offering a break if necessary). These efforts helped to create a safe and comfortable environment where participants felt free and safe to talk about sensitive personal experiences. Ethical respect for the physical, social and psychological well-being of the interview participants was ensured in such situations by showing empathy, sympathy and support; giving assurances of privacy and anonymity and expressing appreciation for their contribution to advancing the research and expanding the knowledge base.

Moreover, given my employment in the pharmaceutical industry, potentially sensitive issues may have arisen in the interviews, concerning conflicts of interest and commercial sensitivities. To avoid these potential issues, I declared all relevant information related to the purpose, benefits, and risks of the interview, and how the data would be managed, to the participants via the Participant Information Sheet (PIS), including the Privacy Notice (see ***Annex 5***). The PIS declared that the information gathered from the interviews would be anonymized, treated as strictly confidential and stored safely on a password-protected computer which only I could access. Furthermore, I disclosed my employment position within the pharmaceutical industry and declared my outsider role in the interviews, as a research instrument and independent enquirer. Moreover, the present study has been conducted independently, with no commercial support from any third party and therefore no conflict of interest is to be declared. The influence of my values and experiences has been restricted to the greatest extent through taking a constant self-reflexive stance and maintaining neutrality, integrity, and transparency throughout the study.

3.9 Summary

This chapter elucidated the research paradigm adopted to address the research questions in the present study. The different approaches to concept analysis and development were scrutinized with regards to their appropriateness for the present research. Rodgers' (1989) evolutionary approach for concept development was adopted and justified for this exploration of PE in medicine development from a value-creation perspective, which includes theoretical, fieldwork and final analytical phases.

An inductive, qualitative, thematic analysis of selected literature in the theoretical phase examined current understandings of the concept of PE in medicine development and produced a provisional thematic map about PE in medicine development to address the RO1 (findings presented in Chapter 4). Empirical data gathered from semi-structured interviews with healthcare stakeholders were interpreted through inductive, qualitative, thematic analysis to address the RO2 (findings presented in Chapter 5). Lastly, the findings from the literature and interviews were triangulated in the final analytical phase to create a comprehensive account of all the qualitative data for a final conceptualization of PE in medicine development from a value-creation perspective to address the RO3 (findings presented in Chapter 6). The analysis and findings from each of the three phases of the study are discussed in greater detail in the next chapters (Chapters 4–6) respectively.

4 Analysis and findings from the theoretical phase

4.1 Introduction

This chapter presents the analysis and findings generated from the theoretical phase of this study, following the research methodological framework designed for the present study based on Rodgers' (1989) evolutional concept development approach (see Chapter 3 and ***Table 5***). The aim of the theoretical phase is to address the first research objective (RO1) – to explore current understandings of the concept of PE in medicine development from a value-creation perspective through a thematic analysis of the literature as data (see Section 1.2). Thereby, themes regarding the antecedents, attributes, consequences, barriers, facilitators, surrogate terms, related concepts, empirical examples of PE in medicine development are identified according to the devised research methodological framework (see Section 3.4). The analysis of literature as data in this chapter is apart from and goes beyond the literature review provided in Chapter 2. Given the lack of results in searching consensus understandings regarding the concept of PE in medicine development from the current literature (as discussed in Section 2.4), the findings presented in this chapter are the results of the qualitative thematic analysis of the eligible 156 literature (see section 3.5.1 and ***Figure 4***), supported by NVivo, to identify emerging themes associated with the key aspects of PE in medicine development inductively. This chapter presents and discusses a provisional thematic map for the concept of PE in the context of medicine development based on thematic analysis of literature data from a value-creation perspective according to Rodgers' (1989) concept development approach.

4.2 Attributes, antecedents, and consequences of PE in medicine development

Drawing on the patient engagement (PE) continuum developed by Carman et al. (2013) and Barello et al. (2012) (as discussed in Section 2.3; ***Figure 2***), the concept of PE in medicine development was analysed from three different yet interrelated perspectives (i.e.

society, patient and PHARMA), representing the key stakeholders involved in the context of medicine development. Contextual factors are an essential element of the evolutionary concept development approach from Rodgers (1989), which considers a concept to be dynamic and context-dependent. Following this principle, the coding of the literature was organized to identify themes concerning antecedents, attributes and consequences of PE in medicine development at the levels of society, the patient and PHARMA respectively, to allow a comprehensive and yet structured account of the concept of PE in medicine development, including the contextual perspectives.

Attributes are the defining characteristics always present in the concept, which describe its fundamental and distinguishing nature; antecedents are the underlying assumptions and prerequisites that must occur or be in place before the concept can take shape, and consequences are the events occurring after the concept – the result of a concept (Rodgers, 1989; Walker & Avant, 2011). Consistent with the concept development approach developed by Rodgers (1989), the antecedences, attributes and consequences of the concept of PE in medicine development were identified in the present study through inductive thematic analysis of the selected literature (see Section 3.6.1). Frequency counts of codes were used to identify the most significant categories and core themes from the data; relationships among these categories and themes were explored with the support of NVivo tools (e.g., using *query* and *explore* tools). The core themes concerning key PE elements in the context of medicine development were developed and documented in a coding book (see ***Annex 8)***. Core themes derived from these thematic analyses are discussed at the different levels (i.e., society, patient, and PHARMA) in the following sections.

4.2.1 Explore PE in medicine development at the society level

Pharmaceutical medicine development endeavours to serve patients and provide healthcare to a society, so the societal perspective of the concept of PE in the context of

medicine development is highly relevant. First, the thematic analysis of the literature data revealed that a paradigm shift to value-based medicine (VBM) is the overarching key antecedent driving the adoption of PE at the society level in medicine development. This overarching key antecedent was derived from three categories: (i) medicine development is driven by patient value; (ii) healthcare issues in innovation and sustainability demand VBM solutions; and (iii) a paradigm shift in healthcare towards VBM (supported by 84 sources with 244 references from the thematic analysis of the literature).

Next, partnership and collaboration were identified as the overarching key defining attribute of the concept of PE in medicine development at the societal level, comprising three categories: (i) shared leadership; (ii) the patient as value co-creator; and (iii) the partnership and collaboration of all healthcare stakeholders (supported by 67 sources with 185 references through the thematic analysis of literature).

Lastly, improved healthcare value was discovered to be an overarching key consequence of PE in medicine development at the societal level, grounded in the categories of (i) improved patient experience; (ii) improved healthcare value; and (iii) improved healthcare sustainability (supported by 58 sources with 113 references through thematic analysis of the literature) (see ***Figure 5***). These identified categories and themes, related to the antecedents, attributes and consequences of PE in medicine development at the societal level, are discussed in detail below.

Figure 5: *Core themes of PE in medicine development at the society level*

4.2.1.1 Attributes of PE in medicine development at the societal level

Key defining attributes of PE in medicine development at the societal level are illustrated in ***Figure 5.1***, supported by collated sources and references generated from the thematic analysis of the literature data (see ***Annex 8***). These identified attributes are elaborated upon below with a focus on their meanings and relationships to each other and to the concept of PE in medicine development at the societal level.

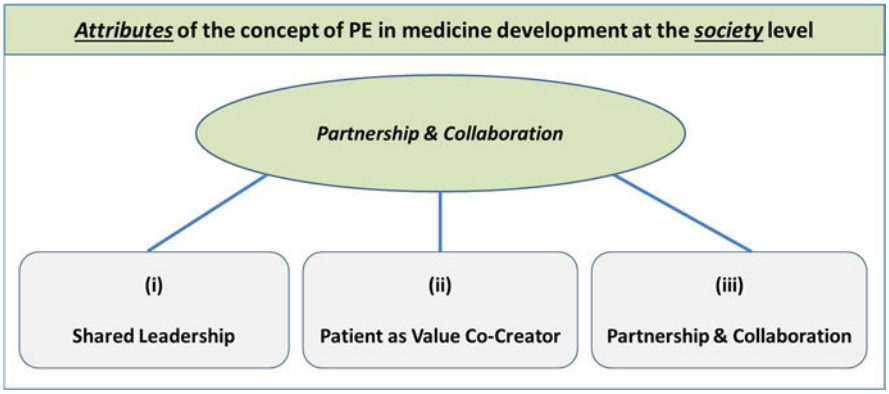

Figure 5.1*: Attributes of PE in medicine development at the society level*

(i) Shared leadership – an attribute of PE in medicine development at the societal level

Patient engagement (PE) at the societal level was frequently described as shared leadership, with joint decision-making in clinical decisions and policy-making (CIHR, 2014; Kelly et al., 2015). It was often depicted as the active engagement of patients with healthcare providers and decision-makers, to create effective, high-quality and sustainable healthcare, which were suggested to be key characteristics of PE in medicine development at the societal level (Barello et al., 2012; Boutin et al., 2017). Carman et al. (2013) attributed the increase in joint decision-making in healthcare policy to the changing role of patients, who were becoming more active, informed and influential, as supported by a growing body of literature (Domecq et al., 2014; Graffigna & Barello, 2015; Perfetto et al., 2017). Furthermore, an increasing number of global and national PE initiatives in clinical settings provided a strong empirical evidence base that shared leadership in decision-making is a key component of the

concept of PE in medicine development at the level of society, suggesting that the patient is becoming an equally valued partner in the context of healthcare and medicine (Batalden et al., 2016; Boudes et al., 2018; CIHR, 2014; Oostendorp, Durand, Lloyd & Elwyn, 2015).

PE in medicine development at the societal level was, thus, understood as the active engagement of patients with HCPs in joint clinical decision- and policymaking (Carman et al., 2013; Barello et al., 2012). The increase in shared leadership with patients within PE at the societal level suggested that patients' needs, preferences and value should guide all clinical encounters and be present in interactions with all healthcare stakeholders, including the medicine development activities within PHARMA (Bae, 2015; Croft & McLoughlin, 2015; Kohler et al., 2017; Laurance et al., 2014).

(ii) <u>Patient as value co-creator</u> - an attribute of PE in medicine development at the societal level

At the level of society, thematic analysis of the literature data revealed that the patient as a value co-creator is another key attribute of PE in medicine development (supported by 23 sources with 54 references from the thematic analysis). Grounded in a VBM paradigm, the notion of the patient as value co-creator reinforces the importance of integrating patients' experience and perspectives into medicine development processes to generate meaningful patient value and healthcare value (Hoos et al., 2015; Kelly et al., 2015; Lowe et al., 2016). The patient as value co-creator was frequently mentioned in the literature as a key attribute of PE in medicine development at the societal level, based on the recognition that patients' experiential knowledge is a valuable asset to be captured within PE in medicine development (Black, 2013; M. T. Brown & Bussell, 2011; Carroll et al., 2017).

From a societal perspective, Bright et al. (2015, p. 643) conceptualized PE in medicine development as 'a gradual process of connection between the healthcare provider and patients in a co-constructed process to generate both positive patient value and

healthcare value', which draws on the notion of the patient as value co-creator as a key attribute of PE in medicine development in this process. Other articles have suggested that patient value, giving essential information about the properties of a medicine from the patients' perspective, should be integrated into the medicine development process with the patient as a value co-creator (Boutin et al., 2017; Loeffler et al., 2013; Sacristan et al., 2016). Thus, PE has been depicted as a co-creation process to generate positive health outcomes with the patient, as a value co-creator, presented as an attribute of PE in medicine development at the societal level (Basch, 2013; Chiauzzi et al., 2016; DIA, 2016; EPF, 2013; Israilov & Cho, 2017; Perfetto et al., 2017; Smith et al., 2016).

The co-creation of positive patient value and healthcare value through interactions between patients and healthcare stakeholders (including PHARMA) draws on the notion that co-creation allows the integration of patient experience in healthcare encounters and maximizes healthcare value, and this is equally applicable in the context of medicine development (Israilov & Cho, 2017). In the co-creation process within PE in medicine development, the patient becomes a value co-creator, actively shaping the medicine development processes, instead of being merely a passive recipient of the medical treatment (Batalden et al., 2016; Bright et al., 2015).

Empirical research from Baines and de Bere (2018) demonstrated that integrating the patient as value co-creator into medical encounters allowed the sharing of information, experience, knowledge and power, which fostered co-learning and increased empowerment and health literacy among patients, thus creating value both for the engaged patients (improved patient value) and healthcare outcomes (improved healthcare value). Consequently, the patient as a value co-creator, was presented as an attribute of PE in medicine development at the societal level.

(iii) <u>Partnership and collaboration</u> - an attribute of PE in medicine development at the society level

Partnership and collaboration were collectively identified as the third key attribute of the concept of PE in medicine development at the societal level (supported by 52 sources with 92 references from the thematic analysis of the literature), drawing on principles of reciprocal respect, trust, co-learning, equality and transparency (Blasimme & Vayena, 2016; EPF, 2013; Frank et al., 2015). An empirical study based on interviews with key healthcare stakeholders by Yeoman et al. (2016) offered evidence of the significance of partnership and collaboration within the concept of PE in medicine development at the societal level, which was endorsed by all participating stakeholders. From a societal perspective, partnership and collaboration within PE in medicine development were described by Kirwan et al. (2017) in another empirical study in areas such as: (i) understanding of patients' wider needs, (ii) co-design of medical solutions and (iii) joint advocacy in the interest of patients. These areas were suggested as key value-adding activities for partnerships and collaboration between PHARMA and patients within PE in medicine development, which would generate positive outcomes for patients and healthcare (Kohler et al., 2017; Messina & Grainger, 2012).

Furthermore, Laurance et al. (2014) illustrated, in an empirical study with four cases, how partnership and collaboration – as a key attribute of PE in medicine development at the societal level – has transformed the role of patients into co-designers of medical solutions in their healthcare through the establishment of an integrated patient advisory council in medicine development processes. Similarly, Blasimme and Vayena (2016) discussed in a scholarly article the significance of partnership and collaboration within PE in terms of facilitating transparency, enforcing accountability and maintaining trust in the area of precision medicine development. Israilov and Cho (2017, p. 1139) suggested in a scholarly article that partnership and collaboration within the concept of PE in medicine development

helped to ‘address hierarchy, overwhelmed patients, and conflicts of interest in health care quality and safety’. Similarly, in a systematic review, Kohler et al. (2017, p. 665) described partnership and collaboration as a key attribute of PE in medicine development at the society level by stating that ‘the active involvement and development of meaningful partnerships that respect the mutual knowledge and expertise of all involved lead to better health care experiences’.

Drawing on the above discussions, shared leadership describes the changing role of patients within healthcare and medicine from passive recipients to equal decision-making partners, which calls for partnership and collaboration with patients within PE in medicine development. The notions of shared leadership and the patient as value co-creator share the common belief that patients’ experiences and knowledge are valuable assets that should be integrated into medicine development though partnership and collaboration within the PE in medicine development. From the above literature findings, *partnership and collaboration* were thus collectively identified as an overarching key attribute of the concept of PE in the context of medicine development at the societal level (see ***Figure 5.1***).

4.2.1.2 Antecedents of PE in medicine development at the society level

Antecedents are the prerequisites that must be in existence before the concept can be present (Rodgers & Knafl, 2000). As presented in ***Figure 5.2***, the key antecedents for the concept of PE in medicine development at the societal level were identified as (i) driven by patient value, which has become the focus of all healthcare stakeholders (S. Davis et al., 2016; Marzorati & Pravettoni, 2017); (ii) healthcare issues of innovation and sustainability demanding an effective solution (Barello et al., 2012; Gurtner & Soyez, 2016); and (iii) a paradigm shift to value-based medicine (VBM) with a re-focus on patient value in healthcare (Marzorati & Pravettoni, 2017; Riva & Pravettoni, 2016).

Further interrogation of the codes and categories identified VBM as a salient overarching key antecedent of PE in medicine development at the societal level, combining the prerequisite events prior to the incorporation of patient value into medicine development within PE (supported by 85 sources and 246 references through thematic analysis of the literature). These identified antecedents for the concept of PE in medicine development at the societal level are discussed further in the following paragraphs.

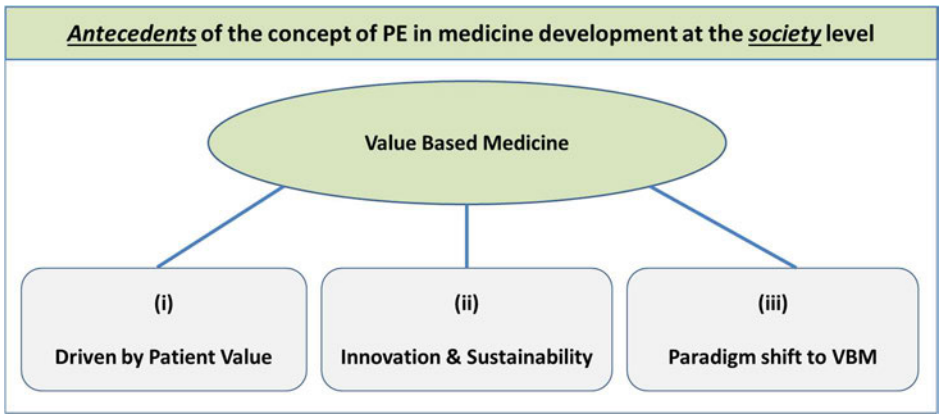

***Figure 5.2**: Antecedents of PE in medicine development at the society level*

(i) Driven by patient value - an antecedent of PE in medicine development at the society level

Patient value is defined as the unique preferences, concerns, and expectations of an individual patient towards medical treatment; and positive results in the patient's outcome, safety and satisfaction at a reasonable and affordable cost (Marzorati & Pravettoni, 2017; Sackett et al., 2000). A broad literature base (supported by 34 sources and 61 references from the thematic analysis) highlighted the consensus that a renewed focus on patient value at the societal level is the driving force causing PHARMA to adopt the concept of PE in medicine development (Boote et al., 2002; S. Davis et al., 2016; Robinson, 2013). A systematic review by Brett et al. (2010) demonstrated that consumerism, patient empowerment and patient centricity were the key factors driving the concept of PE towards focussing on patient value and its integration into medicine development processes. An empirical study based on

consultation with senior healthcare practitioners by du Plessis et al. (2017) demonstrated the significance of patient value in the context of medicine development as a response to an increasingly connected and informed patient population demanding more engagement in the medicine development activities that impact on their lives. Accordingly, the emphasis on patient value by all healthcare stakeholders was considered an important antecedent to PE in medicine development at the societal level.

The increased focus on patient value at the societal level is highly relevant to pharmaceutical medicine development because, if health outcomes are now measured around patient value, PHARMA (as a healthcare provider) needs to demonstrate the presence of patient value in medicine development processes and this will determine the market success of these products (M. T. Brown & Bussell, 2011; Kelly et al., 2015). Based on the above discussions, healthcare stakeholders being driven by patient value was suggested as a key antecedent to PE in medicine development at the societal level.

(ii) <u>Innovation and sustainability</u> - an antecedent of PE in medicine development at the societal level

The literature analysis (supported by 17 sources with 25 references from the thematic analysis) suggested that limited resources in the healthcare system have affected the delivery of high-quality innovation at a sustainable cost. These healthcare issues were suggested as a key trigger for the inclusion of PE in medicine development at the societal level to resolve these healthcare challenges (Barello et al., 2014; Burns et al., 2014; S. Davis et al., 2016). Barello et al. (2014) argued in a literature review that these healthcare issues called for increased PE in medicine development, as PE was expected to have a positive impact on healthcare quality improvement and cost-effectiveness. These arguments concurred with the findings of a literature review conducted by Burns et al. (2014), who reported that healthcare

issues associated with innovation and sustainability were a key driver for PE advancement in medicine development at the societal level.

Furthermore, Davis et al. (2016) revealed in a scholarly article that more than 80 percent of healthcare consumers were dissatisfied with their healthcare experiences; and the adoption of PE in medicine development was considered to be an effective solution in improving the patient experience, treatment outcomes and cost-effectiveness at the societal level, thus addressing the innovation and sustainability issues in healthcare and medicine.

(iii) Paradigm shift to VBM - an antecedent of PE in medicine development at the society level

At the societal level, a paradigm shift in healthcare from a charity model to a new era of VBM was highlighted as a key antecedent for PE in medicine development in a significant amount of literature data (supported by 68 sources with 158 references from the thematic analysis). Further, the paradigm shift to VBM was indicated as a key driving force causing PHARMA to adopt the concept of PE in medicine development to demonstrate patient value within PE (Bae, 2015; M. M. Brown & Brown, 2013; Kohler et al., 2017; Marzorati & Pravettoni, 2017; Riva & Pravettoni, 2016).

A research including four case studies (Laurance et al., 2014) offered further evidence that VBM, with patient value at the core, has become the new healthcare paradigm for the twenty-first century, requiring PE to be adopted in medicine development to deliver the expected positive health outcomes, and thus further substantiating the findings that a *paradigm shift to VBM* is an overarching key antecedent for the concept of PE in medicine development at the societal level (see ***Figure 5.2***).

4.2.1.3 Consequences of PE in medicine development at the society level

The followings were identified as consequences of PE in medicine development at the societal level: (i) PE contributes to an improved patient experience in terms of trust, respect, transparency, legitimacy, relevance, ethical fairness and accountability (EMA, 2017; EPF, 2013; EUPATI, 2016a; Gurtner & Soyez, 2016; IOM, 2012; Kendell et al., 2014; Pushparajah, 2018; Sienkiewicz & van Lingen, 2017); (ii) PE contributes to improved healthcare value in terms of treatment outcomes, quality and efficiency (Bae, 2015; Barello et al., 2012; Chiauzzi et al., 2016; Graffigna & Barello, 2015; Kohler et al., 2017); and (iii) PE contributes to improved healthcare sustainability (Black, 2013; Boutin et al., 2017; Kohler et al., 2017).

Furthermore, *improved healthcare value* was identified as an overarching consequence of the concept of PE in medicine development at the societal level, and was assumed to be the ultimate outcome of PE in medicine development (supported by 58 sources and 113 references in a thematic analysis of the literature). The key evidence and justification for these identified consequences of the concept of PE in medicine development at the societal level are provided in detail in the next paragraphs (see ***Figure 5.3***).

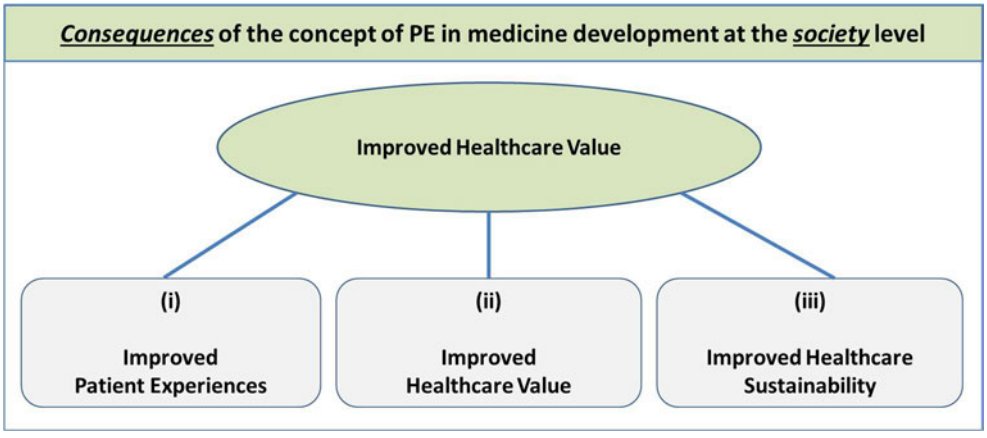

***Figure 5.3**: Consequences of PE in medicine development at the society level*

(i) <u>Improved patient experiences</u> - a consequence of PE in medicine development at the society level

According to a case study conducted by Pushparajah (2018), PE in medicine development was shown to improve healthcare quality and patient experience through shared ambition, transparency, accountability and respect; these positive consequences of PE in medicine development identified at the societal level was very evident in the literature (supported by 19 sources with 24 references). An empirical study based on interviews with patient participants (Kendell et al. 2014) further substantiated the claim that PE in medicine development led to increased trust, legitimacy, relevance and accountability, and that PE in medicine development improved the patient experience overall at the societal level.

Furthermore, effective PE in medicine development was thought to contribute to the legitimacy, relevance and acceptance of healthcare treatment and, thus, PE was strongly recommended in the context of medicine development by various guidance documents issued by health authorities, patient organisations and pharmaceutical associations (EFPIA, 2011; EMA, 2017; EPF, 2013; FDA, 2018a; PhRMA, 2016). These PE-related guidelines further signalled a strong expectation of positive consequences of PE in medicine development at a society level (see ***Figure 5.3***).

(ii) <u>Improved healthcare value</u> – a consequence of PE in medicine development at the society level

Healthcare value is defined from a societal perspective as the health outcomes achieved per dollar spent around the patient (Porter, 2010). A systematic review of healthcare literature conducted by Barello et al. (2012, p. 5) offered evidence that PE may 'contribute to gain better health outcomes, to enhance patient's care and patient experience, to improve illness self-management and adherence to therapies, and to reduce care costs'. A study based on an online survey with 4,000 participants by Chiauzzi et al. (2016) revealed

that personal control and patient's confidence gained through joint decision-making and involvement with PE contributed positively to health outcomes. The positive consequences of PE identified from these two studies align with the findings of Graffigna and Barello (2015, p. 8) whose theoretical research suggested that 'patient engagement allows the improvement of clinical outcomes and patient satisfaction towards the care process'. Similarly, Laurance et al. (2014) offered empirical evidence in a study that PE in medicine development has positively improved patients' health outcomes and reduced costs for healthcare at the societal level.

The assumed positive impacts of PE in medicine development on healthcare outcomes have been widely acknowledged by health authorities (Carroll et al., 2017; M. Y. Smith et al., 2016), health technology assessment (HTA) agents (Frank et al., 2015) and PHARMA (Champagne, Hung & Leclerc, 2015). Furthermore, the expected positive impacts of PE in medicine development on *improved healthcare value* - as a consequence of PE at the societal level - would motivate the adoption of PE in medicine development (supported by 39 sources with 64 references from the thematic analysis) (see ***Figure 5.3***).

(iii) <u>Improved healthcare sustainability</u> - a consequence of PE in medicine development at the society level

It has been extensively suggested in the literature that positive healthcare outcomes, and associated improved healthcare sustainability, can be expected as a consequence of PE in medicine development at the society level (Boutin et al., 2017; Burns et al., 2014; Davis et al., 2016). Boutin et al. (2017) argued in a scholarly article that PE in medicine development helps to improve the identification and prioritisation of the research agenda, developing more relevant solutions to meet patients' needs, and improving the outcomes of healthcare interventions within cost constraints, thus addressing sustainability issues in healthcare.

Burns et al. (2014, p. 8) suggested in a theoretical research that PE in medicine development enabled 'the health system to address the right issues in an appropriate way, design programs, policy and planning activities closely tailored to the needs of both individuals and special populations; achieve better results; and validate outcomes'. Furthermore, Carman et al. (2013, p. 224) reported in a scholarly article that PE in medicine development 'contributes to improvements in quality and patient safety and helps control healthcare costs', thus contributing to healthcare sustainability. Improved healthcare sustainability - as a consequence of PE in medicine development at the society level - was further supported by 17 sources and 25 references from the thematic analysis of literature.

Lastly, further in-depth thematic analysis of the codes and categories derived from the literature revealed that all three identified consequences of PE in medicine development at the societal level (i.e. improved patient experience, improved healthcare sustainability and improved healthcare value) were believed to bring *improved healthcare value* as an overarching consequence associated with PE in medicine development at the society level (supported by 58 sources and 113 references in the thematic analysis of the literature). This finding further illustrated the high societal expectations towards the concept of PE in medicine development, with PE in medicine development being described as 'the blockbuster drug of the century' (Dentzer, 2013; Kish, 2012) able to solve all the critical healthcare issues. Considering the overall evidence from the TA of literature data, *improved healthcare value* was suggested as an overarching core consequence associated with PE in medicine development at the societal level (see ***Figure 5.3***).

4.2.2 Explore PE in medicine development at the patient level

Patients are playing an increasingly important role in pharmaceutical medicine development and are becoming important partners through PE processes. The thematic analysis of the literature suggested the *patient as value co-creator* as an overarching key

attribute of PE in medicine development at the patient level, derived from the categories of (i) the engaged patient, (ii) patient as value co-creator and (iii) presence of the patient voices in medicine development (supported by 88 sources with 245 references in a thematic analysis of the literature data).

Next, acknowledging the *patient as a consumer and expert* was identified as an overarching antecedent to the concept of PE in medicine development at the patient level, grounded in three categories of (i) recognising the patient as a consumer and expert, (ii) respecting patients' rights and ethics, and (iii) improved health literacy and capacity of patients (supported by 67 sources with 133 references in a thematic analysis of the literature).

Lastly, the *improved patient value* was identified as an overarching consequence of PE in medicine development at the patient level, attributed to the three categories of (i) improved adherence and compliance of patients; (ii) improved relevance and adoption of medical solutions by patients; and (iii) improved patient experience and trust (supported by 35 sources with 64 references through a thematic analysis of the literature data). The key codes and themes identified regarding the antecedents, attributes and consequences of PE in medicine development at the patient level, as derived from the thematic analysis of the literature data, are presented in ***Figure 6*** and discussed in detail in the following paragraphs.

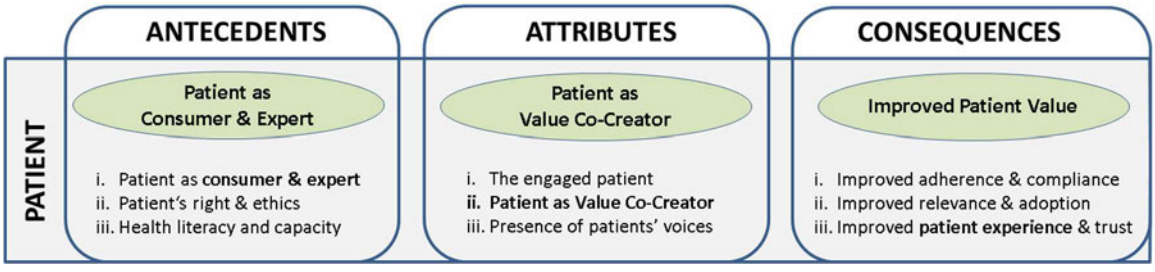

Figure 6*: Core themes of PE in medicine development at the patient level*

4.2.2.1 Attributes of PE in medicine development at the patient level

The defining attributes of PE in medicine development at the patient level, as identified in the theoretical phase in the present study, are: (i) the engaged patients, which describes patients who are pro-active, literate, self-aware, self-efficacious, demanding, connected, organised, with the power to advocate, and who take responsibility for self-management (Barello et al., 2014; Perfetto & Oehrlein, 2015; Hibbard et al., 2004; Marzorati & Pravettoni, 2017; Sacristan et al., 2016; Sharma, 2015); (ii) patient as value co-creator, which describes the notion that patients have a unique asset in their experiential knowledge as healthcare users, which should be brought into the co-creation processes of medicine development (Perfetto & Oehrlein, 2015; Loeffler et al., 2013; Messina & Grainger, 2012; PFMD, 2018a; Shippee et al., 2015; Stegemann et al., 2016; Tapp et al., 2017); and (iii) presence of the patient voices in medicine development within PE, which describes an environment in which patients' voices are heard, understood and integrated into the medicine development processes, so that the products developed address patients' needs and offer real value to them (Black, 2013; Laurance et al., 2014; Riva & Pravettoni, 2016; Tapp et al., 2017).

Furthermore, the *patient as value co-creator* was identified as a salient overarching core attribute of the concept of PE in medicine development at the patient level, through a thematic analysis of the literature data (supported by 88 sources with 245 references). *Patient as value co-creator* - as a broader central theme - connects the ideas of the engaged patient and presence of patients' voices, which were identified as key attributes of PE in medicine development at the patient level (see ***Figure 6.1***).

Patient as value co-creator, identified as an overarching key attribute of PE in medicine development at the patient level, is in alignment with the theoretical core of VCC and SDL which state that customers are always a co-creator of value (Prahalad &

Ramaswamy, 2000; Vargo & Lusch, 2004), thus suggesting the congruence of these theoretical perspectives with the PE phenomenon in medicine development. The identification of the defining attributes of PE in medicine development at the patient level is further discussed and justified below.

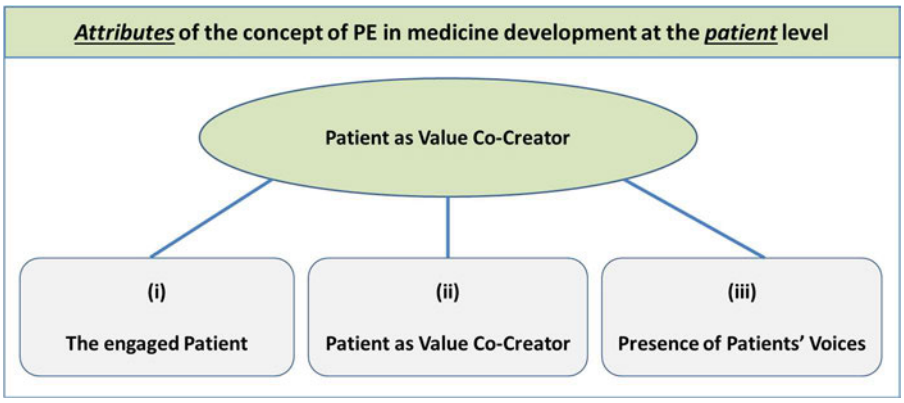

***Figure 6.1**: Attributes of PE in medicine development at the patient level*

(i) The engaged patient - an attribute of PE in medicine development at the patient level

An engaged patient is described as having developed 'specific abilities to interact with the health care system and to make better choices that include value for him or her' (Marzorati & Pravettoni, 2017, p. 104). This description concurs with the conceptualization of PE by Bright et al. (2015, p. 648) that patient engagement is 'a process and a state influenced by both the intrinsic variables within the patients such as willingness, self-efficacy and outcome expectations, and their social and physical environment'. An engaged patient was further described as active, literate and having the power to advocate (Barello et al., 2014). Next, being self-aware, self-efficacious, active and willing to take responsibility for their self-management were qualities suggested by several scholars as key attributes of an engaged patient within the concept of PE in medicine development at the patient level (Hibbard et al., 2004; Sacristan et al., 2016; Sharma, 2015). An empirical study, based on interviews with patients (n=42) suffering from chronic disease, by Sheridan et al. (2015) offered evidence that two-thirds of patients were willing to be engaged and take a more

active role in PE if they were properly informed. Additionally, engaged patients within PE in medicine development were shown to have related improved healthcare outcomes (Barello et al., 2015; Carman & Workman, 2017; Koh et al., 2013).

Moreover, an increasing body of literature has indicated the growing role of patient organisations (POs) in representing patients' interests on a collective level for the purposes of advocacy, capacity building, peer support and participation in medicine development (Bloom et al., 2018; Perfetto & Oehrlein, 2015; Sacristan et al., 2016; Sienkiewicz & van Lingen, 2017). The presence of POs was shown to have significantly enhanced patients' advocacy power and facilitated more organised PE in medicine development (S. K. Smith et al., 2015). Patient organisations (POs) are defined (EPF, 2013, p. 3) as 'not-for-profit organisations which are patient-focused, and whereby patients and/or carers (the latter when patients are unable to represent themselves) represent a majority of members in governing bodies'. The engaged patient, as a key attribute of PE in medicine development at the patient level, was further supported by 55 sources with 144 references from the thematic analysis of the literature data in the present study (see ***Figure 6.1***).

(ii) <u>Patient as value co-creator</u> - an attribute of PE in medicine development at the patient level

Acknowledging the patient as a value co-creator was identified as another key attribute of PE in medicine development at the patient level (supported by 55 sources with 91 references in a thematic analysis of the literature data). This attribute of PE in medicine development at the patient level was built on the consensus that patients' experiential knowledge of living with a disease is a valuable asset and patients have the right to be involved in the medicine development processes which impact on their lives (Perfetto & Oehrlein, 2015; Messina & Grainger, 2012; PFMD, 2018a).

An empirical study conducted by Messina and Grainger (2012, p. 200) revealed that patients' experience can offer valuable insight, helping the evaluation of medicine 'to move beyond a *technical exercise* that considers mainly quantitative evidence that is free from values and ethical judgements'. A systematic review by Shippee et al. (2015) suggested that reciprocal relationships and co-learning were the key attributes of value co-creation (VCC) processes within PE in medicine development, from both ethical and value-adding perspectives. Similarly, the notion of the patient as a value co-creator within PE in medicine development was conceptualized by Stegemann et al. (2016, p. 1049) as 'the recognition of the needs of an individual patient or distinct patient populations and their specific needs as the focal point in the overall design of a medicine including the targeted patients' physiological, physical, psychological, and social characteristics'. Further, an empirical case study by Tapp et al. (2017) examined the variety of roles played by patients within PE in medicine development, and their impacts on the study outcome, which suggested that patients can co-create value throughout the medicine development processes in co-prioritisation, co-planning, co-implementation, co-dissemination and co-measurement.

To summarise, the notion of the patient as value co-creator – as a key attribute of the concept of PE in medicine development at the patient level – was further substantiated by a broad base of evidence in the literature (S. Davis et al., 2016; de Wit et al., 2017; Kohler et al., 2017; Sienkiewicz & van Lingen, 2017) (see ***Figure 6.1***).

(iii) <u>Presence of patient voices</u> - an attribute of PE in medicine development at the patient level

Hoos et al. (2015) argued in a scholarly article that the purpose of medicine is to improve patients' lives; thus, effective PE is needed to ensure that patients' needs, and priorities can be identified and met through the presence of the patient voices throughout the medicine development, regulatory approval and market access decisions. Boudes et al. (2018)

further substantiated the presence of the patient voices as a key attribute of PE in medicine development with an empirical study based on interviews with healthcare stakeholders. A more detailed account of how to incorporate patients' voices in medicine development within PE at a patient level was offered by Sacristan et al. (2016) in a scholarly article in the areas of prioritising the research agenda, study design, access to clinical trials, incorporating patient experience and dissemination of research results. Additionally, Smith et al. (2016) argued in a scholarly article that PE has a strategic imperative to introduce the patient voices in the benefits and risks assessment of medicines and that patient voices is a core element linking patients' needs with product profiles in medicine development. As a result, the presence of patient voices as a key attribute of PE in medicine development at the patient level was further supported by 9 sources with 9 references from the thematic analysis of the literature data in the present study.

Additionally, the identified codes and categories regarding the attributes of PE in medicine development at the patient level were further compared and examined to seek core themes across the dataset. In this process, the *patient as value co-creator* was identified as a salient overarching central core attribute of the concept of PE in medicine development at the patient level (supported by 87 sources with 244 references in a thematic analysis of the literature data) (see ***Figure 6.1***).

4.2.2.2 Antecedents of PE in medicine development at the patient level

The following antecedents of the concept of PE in medicine development at the patient level were identified from the theoretical phase: (i) recognising the patient as a consumer and expert with experiential knowledge of living with disease (Hoos et al., 2015; Mitchell et al., 2017; Newman & Vidler, 2006); (ii) recognising patients' rights and ethics regarding PE in medicine development (Perfetto et al., 2015; Dewulf, 2017; du Plessis et al., 2017); and (iii) recognising patients' health literacy and capacity associated with PE in

medicine development (Batalden et al., 2016; Blasimme & Vayena, 2016; Bloom et al., 2017). Furthermore, recognising the *patient as a consumer and expert* was identified as an overarching core antecedent of PE in medicine development at the patient level, which was suggested as a central organising theme that connects the other antecedents (supported by 67 sources with 139 references through a thematic analysis of the literature) (see ***Figure 6.2***). These identified antecedents for the concept of PE in medicine development at the patient level are further discussed and justified in the following paragraphs.

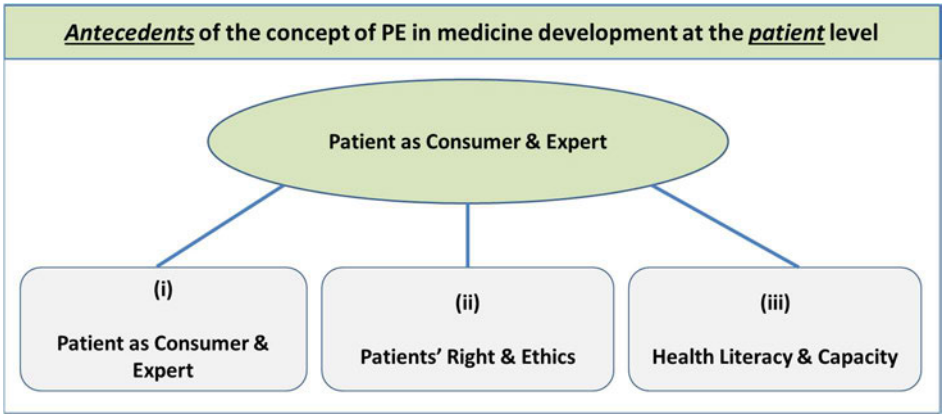

Figure 6.2*: Antecedents of PE in medicine development at the patient level*

(i) Patient as consumer and expert - an antecedent of PE in medicine development at the patient level

In a scholarly article, Robinson and Ginsburg (2009, p. 278) discussed the origin and development of consumerism in healthcare and medicine by stating that 'healthcare should be consumer-driven for reasons of both efficiency and ethics', indicating the transformation of healthcare and medicine into a domain of personal rights and choices instead of collective paternalism. Similarly, Hoos et al. (2015) argued in another scholarly article that patients' aspirations and journeys were as important as the treatment options; thus, patients should be put at the centre of healthcare and medicine as beneficiaries and customers. Empirical research based on interviews and case studies by Newman and Vidler (2006) suggested further that consumerism in healthcare and medicine needs responsive healthcare services

and medicinal products, designed to meet the individual patient's needs and benefits rather than the convenience of the producers.

Patients' increasing dissatisfaction with healthcare performance (e.g., due to high healthcare costs, mistrust of PHARMA, poor healthcare service quality) was another factor driving patients to demand greater engagement in healthcare and medicine development processes that would impact their lives (Kirwan et al., 2017). Davis et al. (2016) argued in a scholarly article that the shifting of healthcare and medicine into consumerism requires all healthcare stakeholders to appreciate patients' experiential knowledge and cooperate with patients as consumers and experts, in researching their diseases and developing medicines. Moreover, Mitchell et al. (2017) illustrated in a scholarly article that pharmaceutical medicine development is undergoing a radical shift towards PE, driven by increasingly informed, knowledgeable, and empowered patients, who demand engagement at every step of the medicine development processes affecting them. The new role of the patient as consumer and expert within PE in medicine development was discussed by Kirwan et al. (2017, p. 482), who commented that 'the personal experiential knowledge of living with their condition adds to the theoretical and empirical knowledge of researchers and clinicians'. Additionally, Blasimme and Vayena (2016, p. 2) observed that the 'patient is an enormous repository of information that needs to be harvested as a partnership not only in clinical care but in discovery'.

A broad range of literature suggested that patients' experiential knowledge of living with a condition was the most powerful asset and resource they could bring and should be integrated into medicine development processes within PE (Dewulf, 2015; Perfetto & Oehrlein, 2015; Loeffler et al., 2013; Sienkiewicz & van Lingen, 2017; von Tigerstrom, 2016). Therefore, recognising the patient as consumer and expert was suggested as a key antecedent for the concept of PE in medicine development at the patient level, as further

evidenced in the thematic analysis of the literature in the present study (supported by 21 sources with 25 references) (see ***Figure 6.2***).

(ii) <u>Patients' right and ethics</u> - an antecedent of PE in medicine development at the patient level

WHO (1978) made a clear statement (principle IV) about patients' rights and participation in healthcare by stating that 'the people have the right and duty to participate individually and collectively in the planning and implementation of their healthcare', and many social and political scholars agreed, calling for a redistribution of power between lay users and medical experts as a prerequisite to the concept of PE in medicine development (Duffett, 2017; DIA, 2015; Lavallee et al., 2012; Sienkiewicz & van Lingen, 2017). Accordingly, patients should be involved in all the healthcare processes which might affect them, including medicine development (Deverka et al., 2012; von Tigerstrom, 2016). A broad consensus was reached among scholars and practitioners that the patient's participation in medicine development is required from an ethical and moral perspective, and deemed necessary to enhance transparency, respect, autonomy and the legitimacy of decision-makings related to patients' lives (Domecq et al., 2014; Grande et al., 2014).

Furthermore, a scholarly article based on discussions with regulators, patients and PHARMA by DIA (2015, p. 2) came to the conclusion that 'for a medical product to truly meet the needs of the patient for whom it is intended, its benefits and risks must be balanced in the context of the patient's perspective, making patient input central to benefit-risk decision-making'. Consequently, acknowledging patients' right and ethics - as an antecedent to the concept of PE in medicine development at a patient level - was widely supported by both scholars and practitioners (Blasimme & Vayena, 2016; EPF, 2013; EUPATI, 2016c; M. Y. Smith et al., 2016), and substantiated further by 12 sources with 18 references from the thematic analysis of the literature in the present study (see ***Figure 6.2***).

(iii) <u>Patients' health literacy and capacity</u> – an antecedent of PE in medicine development at a patient level

Digitalisation and the explosion of health information on the internet were widely acknowledged as factors which have significantly increased patients' health literacy and capacity since the early twenty-first century (Croft & McLoughlin, 2015; Milani & Franklin, 2017). A wide range of literature indicated the positive association between increased patient health literacy and the global proliferation of self-management and shared decision-making attributes associated with the concept of PE in healthcare and medicine (Barello et al., 2014; Carroll et al., 2017; Dentzer, 2013; Koh et al., 2013; Messina & Grainger, 2012). A survey conducted by Champagne et al. (2015) revealed that 85 percent of patients were confident to take part in PE in medicine development, provided that medical information was accessible to support their health literacy.

Increasingly, patient organisations (POs) have contributed to the improved health literacy and capacity building of patients through providing systematic medical training and establishing trained patient researcher networks, which have been shown to have positive influences on PE in empirical studies by de Wit et al. (2017) and Bloom et al. (2018). Furthermore, several scholarly articles suggested that PHARMA should provide more medical education and patient support programmes to support the health literacy and capacity of patients in their self-management journey and in participating in research, and these programmes were indicated as prerequisites for effective PE in medicine development at the patient level (Berger et al., 2014; Dewulf, 2015; Duffett, 2017; Miseta, 2015a; Mitchell et al., 2017; Richard et al., 2017; Sacristan et al., 2016). As a result, the notion of increased patients' health literacy and capacity as an antecedent for the concept of PE in medicine development at the patient level was supported by 50 sources with 90 references from the thematic analysis of the literature data.

Furthermore, an in-depth examination of the codes and categories regarding the antecedents of PE at the patient level suggested recognising the *patient as consumer and expert* as a salient overarching core antecedent to the concept of PE in medicine development at the patient level (supported by 67 sources with 139 references through a thematic analysis of the literature). This implies that, only when PHARMA treats patients, rather than prescribing physicians, as their primary consumer and recognises that patients are experts in their diseases, can authentic PE in medicine development become reality. This belief was extensively supported in the literature (Dewulf, 2015; du Plessis et al., 2017; Mitchell et al., 2017; Sienkiewicz & van Lingen, 2017) (see ***Figure 6.2***).

4.2.2.3 Consequences of PE in medicine development at a patient level

The following consequences of PE in medicine development at the patient level were identified in the theoretical phase (see ***Figure 6.3***): (i) improved adherence and compliance (Barello et al., 2015; CIHR, 2014; Dentzer, 2013); (ii) improved relevance and adoption of developed medicinal products (Carroll et al., 2017; de Wit et al., 2017; Getz, 2015); and (iii) improved patient experience and trust (Danis & Solomon, 2013; Dewulf, 2015; Israilov & Cho, 2017; Ayton et al., 2018).

Moreover, *improved patient value* was identified as a salient overarching core theme concerning the consequence of PE in medicine development at the patient level and was indicated as the underlying thread weaving all the other consequences together, since all these consequences were supposed to lead to improved patient value as an ultimate consequence (as supported by 35 sources with 64 references in a thematic analysis of the literature) (see ***Figure 6.3***). These identified consequences of the concept of PE in medicine development at the patient level are further elaborated and justified in the next paragraphs.

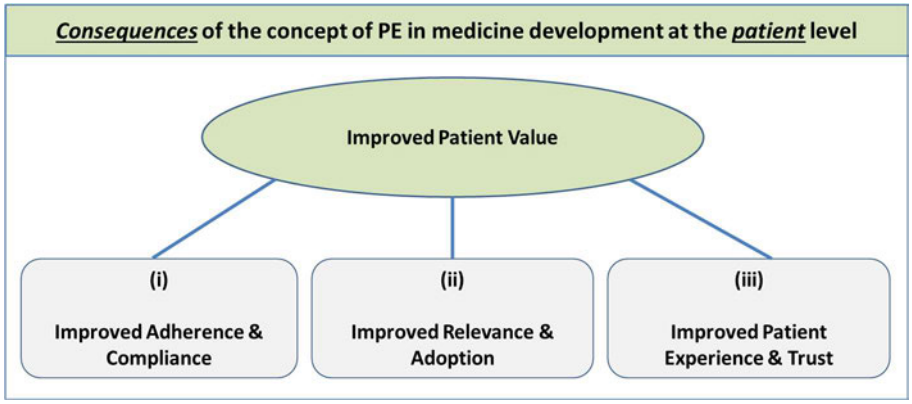

***Figure 6.3**: Consequences of PE in medicine development at the patient level*

(i) Improved adherence and compliance - a consequence of PE in medicine development at the patient level

Evidence of the consequences of PE in medicine development at the patient level was arguably strongest regarding the improved adherence and compliance with the therapies, leading to better health outcomes, and it has been suggested that this is a direct result of the positive cognitive and behavioural changes of an engaged patient (Barello et al., 2012; Barello et al., 2015; Birnbaum, Lewis, Rosen & Ranney, 2015; Hibbard & Mahoney, 2010). A systematic review by Berger et al. (2014) demonstrated evidence of the positive effects of PE in medicine development on the increased adherence of patients to a prescribed treatment, thus contributing to the safety and effectiveness of the treatment outcome.

Furthermore, Laurance et al. (2014) provided evidence, following an empirical study with four real cases, for the beneficial consequences of PE in medicine development in terms of improving patients' compliance with the therapy, thus improving health outcomes and reducing costs. Improved adherence and compliance - as a consequence of PE in medicine development at a patient level - was supported by 24 sources with 38 references from the thematic analysis of the literature in the present study (see ***Figure 6.3***).

(ii) <u>Improved relevance and adoption</u> - a consequence of PE in medicine development at the patient level

In a literature review, Carman and Workman (2017) suggested a positive link between PE in medicine development and the increased adoption of patient-relevant medicinal solutions, thus leading to improved health outcomes. Furthermore, Shippee et al. (2015), in a systematic review, highlighted the positive consequences of PE in medicine development in terms of improved applicability and the adoption of developed medicinal products, in line with a number of other studies (Akhmetov & Bubnov, 2017; Deverka et al., 2012; Frank et al., 2015; Getz, 2015).

Further, Carroll et al. (2017) conducted an empirical study involving survey and interviews (*n*=54) with a clinical research network, which confirmed the increased relevance and adoption of research results as a consequence of PE in medicine development. Moreover, two studies involving interviews with practitioners in medicine development, by Crawford et al. (2017) and Perfetto and Oehrlein (2015), offered further evidence that effective PE in medicine development contributed to an optimal study design and improved study outcomes, because PE allowed the patients' needs to be captured, and thus facilitated the practical adoption of medicinal products which were jointly developed with patients through PE in medicine development. As a result, improved relevance and adoption of medicine as a consequence of PE in medicine development at a patient level was substantiated by 8 sources with 10 references from the thematic analysis of the literature (see ***Figure 6.3***).

(iii) <u>Improved patient experience and trust</u> - a consequence of PE in medicine development at the patient level

A substantial body of literature argued for improved patient experience and trust associated with improved psychological and behaviour states, better health outcomes and greater satisfaction as consequences of PE in medicine development at the patient level

(Akhmetov & Bubnov, 2017; Armstrong, Mullins et al., 2017; Ayton et al., 2018; Barello et al., 2014; CIHR, 2014; Danis & Solomon, 2013; Getz, 2017; Hibbard & Mahoney, 2010). An empirical study investigating the correlation between PE in medicine development and positive patient experience, conducted by Sebastian, Ramos, Stumbo, McGrath and Fairbrother (2014), demonstrated a positive association between the two events. Theoretical research by Dewulf (2015), exploring the impacts of PE, revealed that PE in medicine development positively influenced the patient journey (i.e. healthy behaviour, positive experiences, increased confidence, trust and commitment) and led to improved healthcare results, which increased the satisfaction and trust of patients regarding the medicinal products. Israilov and Cho (2017) discussed in a scholarly article the causal relationship between PE and the consequences of satisfaction, trust, relationship strength, attitudinal and behavioural loyalty of patients, and substantiated the significance of PE in medicine development as a concept generating positive patient experience and trust. This claim was further supported by 13 sources with 16 references generated from a thematic analysis of the literature (see ***Figure 6.3***).

Additionally, codes and categories related to the consequences of PE in medicine development at the patient level were further examined to search for commonality and patterns. As a result, *improved patient value* was identified as an overarching core theme concerning consequence of PE in medicine development at the patient level (supported by 35 sources with 64 references in a thematic analysis of the literature). It was further argued that, ultimately, any improvement in the adherence and compliance of patients, improved relevance and adoption of the medicinal product, or improved patient experience and trust would inevitably lead to improved patient value, which should be an overarching measurable consequence associated with PE in medicine development at the patient level (Duffett, 2016; Hoos et al., 2015; Hunter et al., 2015; NEJM, 2017) (see ***Figure 6.3***).

4.2.3 Explore PE in medicine development at the PHARMA level

While a large volume of academic literature explores the concept of PE from different disciplinary perspectives in the context of healthcare, a systematic conceptualization of the concept of PE in the specific context of medicine development at the PHARMA level was missing in the current knowledge base (Domecq et al., 2014; Lowe et al., 2016; Perfetto et al., 2017). PHARMA operates in the healthcare environment with the primary aim of developing medicinal products which can improve patient health outcomes and contribute to an improved patient value and healthcare value, while maintaining business success (Croft & McLoughlin, 2015; Bloom et al., 2018). Therefore, with an increased demand for PE in medicine development by both patients and the society (as discussed in Section 4.2.1 and 4.2.2), the concept of PE has been now introduced into the medicine development at PHARMA with ever-increasing significance (Lowe et al., 2016; Hahn et al., 2017; Mitchell et al., 2017; Boudes et al., 2018).

Core themes related to the concept of PE in medicine development at the PHARMA level were explored through a thematic analysis of the literature data. As a result, the *integration of patient value* was identified as an overarching key attribute of the concept of PE in medicine development at the PHARMA level (supported by 94 sources with 296 references in a thematic analysis of the literature). Next, *patient centricity* was identified as an overarching key antecedent for the concept of PE in medicine development at the PHARMA level (supported by 82 sources with 144 references in a thematic analysis of literature). Lastly, an *improved business value* was suggested as an overarching key consequence of the concept of PE in medicine development at the PHARMA level (supported by 64 sources with 168 references in a thematic analysis of the literature) (see ***Figure 7***). These identified attributes, antecedents, and consequences for the concept of PE in medicine development at the PHARMA level are further discussed and justified below.

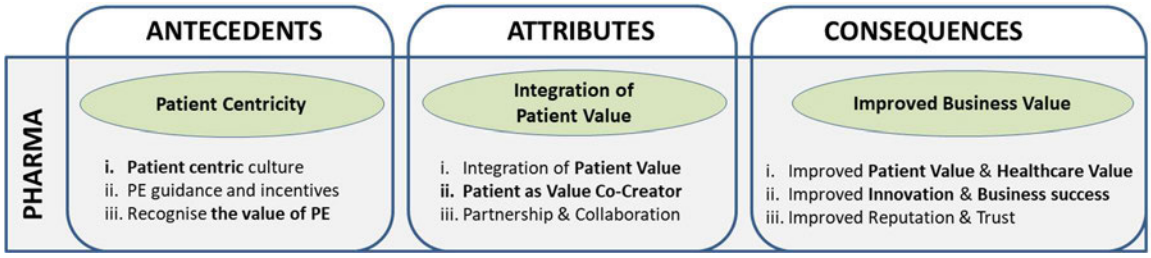

***Figure** 7: Core themes of PE in medicine development at the PHARMA level*

4.2.3.1 Attributes of PE in medicine development at the PHARMA level

The defining attributes of PE in medicine development at the organisational level (i.e. at the PHARMA level for the present study) were identified from the theoretical phase as follows: (i) integration of patient value throughout the medicine development processes (Boudes et al., 2018; Lowe et al., 2016; Perfetto et al., 2017); (ii) the patient as value co-creator with patient involvement through interactions (de Wit et al., 2017; Duffett, 2017; Kirwan et al., 2017); and (iii) partnership and collaboration following the principles of meaningful PE: effective, systematic, reciprocal, trustful, ethical and value-adding (Kohler et al., 2017; Pushparajah, 2018; Stegemann et al., 2016; Yeoman et al., 2016). Furthermore, the integration of patient value was identified as an overarching core attribute of the concept of PE in medicine development at the PHARMA level (supported by 94 sources with 296 references through a thematic analysis of the literature) (see ***Figure 7.1***). The integration of patient value (referring to a means of interaction with patients to incorporate patient input, experience and needs into the medicine development life-cycle) was grounded in the recognition of patient as value co-creator, adopting a partnership and collaboration attitude by PHARMA (as sub-categories), which must be present as key attributes of PE in medicine development at the PHARMA level (Chiauzzi et al., 2016; Kelly et al., 2015; Smith et al., 2015). These defining attributes for the concept of PE in medicine development at the PHARMA level are further elaborated and justified in the following paragraphs.

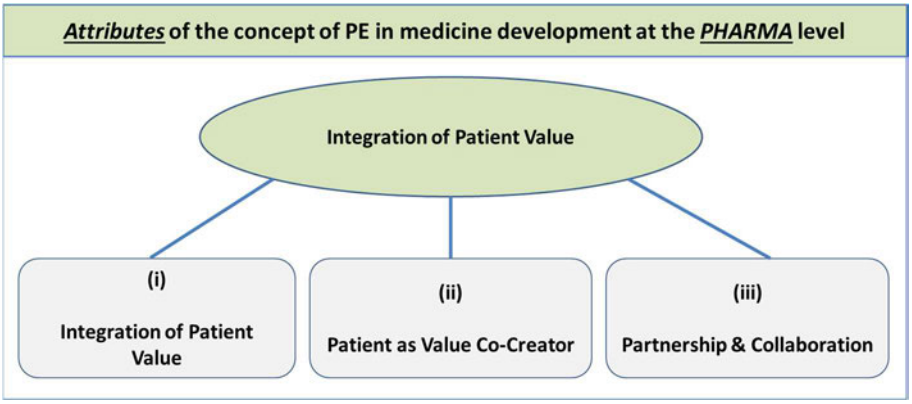

***Figure 7.1**: Attributes of PE in medicine development at the PHARMA level*

(i) Integration of patient value - an attribute of PE in medicine development at the PHARMA level

Pharmaceutical companies (PHARMA) are tasked with 'developing life-changing products that meet the needs of patients, physicians, and payers while adhering to regulatory standards, managing health technology and payer scrutiny, and performing to satisfy investors' (Lowe et al., 2016; p. 869). The complex spectrum of tasks that PHARMA covers may include potentially conflicting aims as it serves different stakeholders with different interests (Bloom et al., 2018). In an empirical study involving interviews with PHARMA experts, Lowe et al. (2016) argued that in an era of patients becoming consumers and healthcare value being measured around patient value, PHARMA needs to incorporate patient value into the medicine development process. Integration of patient value in medicine development was, therefore, argued to be a key attribute for the concept of PE in medicine development at the PHARMA level (Boudes et al., 2018; Perfetto et al., 2017). Recently, Boudes et al. (2018) suggested, in an empirical study involving a survey and interviews (n=59) with healthcare stakeholders, that the key attribute of PE in medicine development is to capture patients' needs and incorporate patients' views by the integration of patient value, which includes sub-elements of (i) interactions, (ii) capturing patient input and (iii) understanding patients' needs and experiences. Furthermore, the integration of patient value as a key attribute of PE in medicine development at the PHARMA level has been

substantiated by various scholarly articles (Basch, 2013; Perfetto & Oehrlein, 2015; M. Y. Smith et al., 2016), systematic reviews (Bright et al., 2015; Burns et al., 2014) and empirical studies (Birnbaum et al., 2015; Duffett, 2017; Kirwan et al., 2017; Lowe et al., 2016; Stegemann et al., 2016; Yeoman et al., 2016). In the present study, the integration of patient value as a key attribute of PE in medicine development at the PHARMA level was further supported by 40 sources with 61 references from a thematic analysis of the literature (see ***Figure 7.1***).

(ii) <u>Patient as value co-creator</u> - an attribute of PE in medicine development at the PHARMA level

An empirical study based on interviews with patients and pharmaceutical experts (*n*=22) by Yeoman et al. (2016) suggested that recognising the patient as a value co-creator is a key attribute of the concept of PE in medicine development, allowing PHARMA to understand patients' wider needs and co-design medical solutions with patients, rather than on patients. Additionally, several other studies have highlighted that the patient as a value co-creator – as a key attribute of PE in medicine development at the PHARMA level – covers aspects including (i) clinical trial co-design and patient recruitment (Holm et al., 2016; S. K. Smith et al., 2015); (ii) benefits and risks assessment (BRA) from patients' perspectives (DIA, 2015; M. Y. Smith et al., 2016); (iii) patient-reported outcomes (PRO) and real-life evidence generation (Black, 2013; Coons et al., 2015). Moreover, the patient as value co-creator within PE in medicine development was further characterized through interactions, partnership and collaboration between PHARMA and POs, representing and expressing the collective views of a patient population on a specific issue or disease area (de Wit et al., 2017; Duffett, 2017; Kirwan et al., 2017).

In recent years, increasing numbers of scholarly articles have been published demonstrating that the patient as value co-creator is further enhanced through systematic

interactions between PHARMA and POs in the context of medicine development (Bloom et al., 2018; Crawford et al., 2017; Sienkiewicz & van Lingen, 2017). PE, as a process for PHARMA to co-create value with the patient, in the context of medicine development has recently been extensively debated in both the medicine domain (Akhmetov & Bubnov, 2017; Boudes et al., 2018; Croft & McLoughlin, 2015; Perfetto et al., 2017) and the management domain (Dubois et al., 2016; Yeoman et al., 2016). At its core, the notion of the patient as a value co-creator is seen as a company's appreciation of the knowledge and experience of patients that can be integrated into medicine development processes to create value for all involved (Loeffler, 2013; NEJM, 2017).

The idea of the patient (i.e. customer) as a value co-creator is rooted in the VCC theory which has been widely applied in fields of management and marketing across other industries for decades (Parks, Baker & Kiser, 1981). More recently, the patient as a value co-creator – as a key attribute of PE in medicine development at the PHARMA level – has been suggested in a wide range of medicine and healthcare literature (de Wit et al., 2017; Duffett, 2017; Israilov & Cho, 2017; Loeffler et al., 2013; Pushparajah, 2018), as supported further by 82 sources with 200 references from the thematic analysis of the literature in the present study (see ***Figure 7.1***).

(iii) <u>Partnership and collaboration</u> - an attribute of PE in medicine development at the PHARMA level

As well as defining the content attributes, related to what PE means in the context of medicine development, several process attributes were debated in the literature, describing how PE should take place at the PHARMA level, and these were considered as important as the content attributes concerning PE in medicine development (Kohler et al., 2017; Pitts, 2016). Lavallee, Tambor, Williams and Deverka (2012) proposed that partnership and collaboration are further key process attributes for the concept of PE in medicine

development at the PHARMA level, emphasizing the process principles of respect, trust, legitimacy, fairness, competence, and accountability. These proposed PE process principles in medicine development resonate with other studies, suggesting that a meaningful PE should have the process attributes of legitimacy, fairness, accountability, mutual contribution and benefits, transparency, reciprocal respect, trust, compassion, ethics, system and efficacy (CIHR, 2014; Perfetto & Oehrlein, 2015; IMI, 2018). Those process attributes at the PHARMA level represent an effective PE in medicine development, based on authentic partnership and collaboration between PHARMA and patients (Kohler et al., 2017; NHC, 2015a; PhRMA, 2016; Yeoman et al., 2016).

In the present study, the following six key partnership and collaboration principles regarding PE in medicine development were identified from the theoretical phase (supported by 15 sources with 29 references in a thematic analysis of the literature): PE in medicine development should be (i) effective, i.e. it generates meaningful outcomes and improved experiences for patients (Deverka et al., 2012; Lavallee et al., 2012; Yeoman et al., 2016); (ii) systematic, i.e. it is not a one-off effort, but rather a continuous series of interactions based on a meaningful, data-driven, structured approach (PhRMA, 2016; Pitts, 2016); (iii) reciprocal, i.e. there are mutual contributions and benefits (Kohler et al., 2017; NHC, 2015a); (iv) trustful, i.e. showing respect, compassion, openness, transparency, having shared goals and accountability (Perfetto & Oehrlein, 2015; Yeoman et al., 2016); (v) ethical, i.e. considering the aspects of inclusiveness, participatory ethics and legitimacy of patients as healthcare consumers (CIHR, 2014; NHC, 2016; Richard et al., 2017) and (vi) adding mutual value, i.e. meaningful PE should generate mutual benefits for both patients and PHARMA to ensure sustainability (Perfetto et al., 2017; Pushparajah, 2018; Stegemann et al., 2016). These guiding principles of PE in medicine development based on partnership and

collaboration, were suggested as crucial process attributes of PE in medicine development at the PHARMA level to enable authentic PE in medicine development (see ***Figure 7.1***).

4.2.3.2 Antecedents of PE in medicine development at the PHARMA level

As illustrated in ***Figure 7.2***, the following antecedents of the concept of PE in medicine development at the PHARMA level were identified from the theoretical phase: (i) a patient-centric culture and strategy (Boutin et al., 2017; S. Davis et al., 2016; Hoos et al., 2015; Jackson, 2016; Pushparajah, 2018); (ii) PE guidance and incentives within an ethical, social, legal (ESL) and regulatory framework (Adams & Petersen, 2016; Bloom et al., 2018; Burns et al., 2014; Dewulf, 2015; S. K. Smith et al., 2015) and (iii) recognition of the value of PE in medicine development by PHARMA (Akhmetov & Bubnov, 2017; Batalden et al., 2016; Croft & McLoughlin, 2015; du Plessis et al., 2017). Furthermore, *patient centricity* was identified as an overarching core theme concerning antecedent for the concept of PE in medicine development at the PHARMA level through a thematic analysis of the literature (supported by 52 sources with 146 references).

Patient centricity (referring to a company's strategy and culture in which the needs of patients and carers are as important to a company's thinking and actions as the need for profit, permeating and informing all aspects of business) was suggested as an overarching core antecedent to an authentic PE in medicine development at the PHARMA level (Mitchell et al., 2017), which was supported by patient-centric culture, PE guidance and incentives, and the recognition of the value of PE (identified as sub-categories) at the PHARMA level (Bloom et al., 2018; Duffett, 2017; Yeoman et al., 2016; Wilson et al., 2018). These identified antecedents of the concept of PE in medicine development at the level of PHARMA are further elucidated and justified in the following paragraphs.

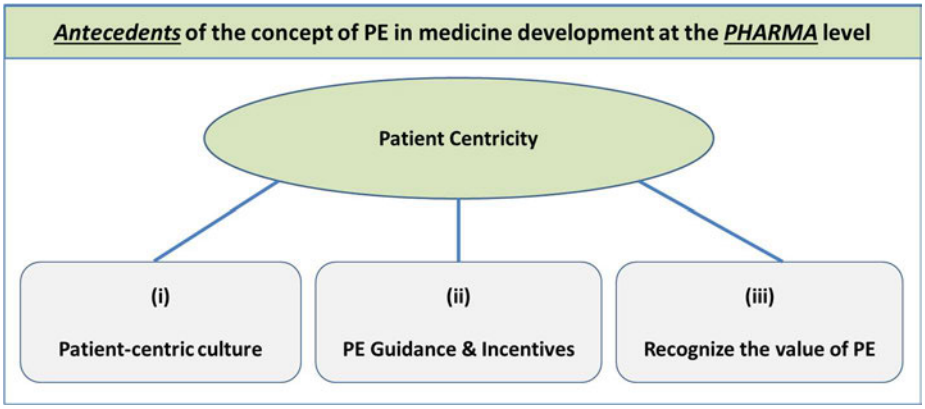

***Figure 7.2**: Antecedents of PE in medicine development at the PHARMA level*

(i) Patient-centric culture - an antecedent of PE in medicine development at the PHARMA level

PHARMA has been repeatedly criticized in the literature as not yet ready to engage with patients in medicine development processes, and the PE activities of PHARMA have frequently been described as mere tokenism, making only a symbolic effort (Hahn et al., 2017; Hall et al., 2018; Lowe et al., 2016). Boutin et al. (2017) argued that establishing a patient-centric culture at the PHARMA level was the prerequisite to facilitating the implementation of PE in medicine development. Several influencing factors were identified in the literature as the key drivers forcing PHARMA to adopt a patient-centric culture within PE in medicine development: (i) healthcare and medicine were moving towards a value-based system with patient value at its core, thus PHARMA would need to engage with patients as customers to deliver patient value and healthcare value (Pushparajah, 2018; R. Robinson, 2013; Sartori et al., 2016); (ii) the increasing demands of a predictive, personalised, preventive, participatory, and psycho-cognitive (P5) medical model to treat patients were associated with the participatory role of patients as research partners in medicine development (Blasimme & Vayena, 2016; S. Davis et al., 2016; Sharma, 2015); and (iii) increasing evidence demonstrating the benefits of PE in medicine development in helping PHARMA to achieve its triple aim of innovation, addressing unmet needs and

achieving a return on investment (ROI) (Carman & Workman, 2017; Croft & McLoughlin, 2015; CUTTINGEDGE, 2016). Taking the above arguments into account, the adoption of a patient-centric culture by PHARMA was deemed a necessary prerequisite for introducing PE into medicine development at the PHARMA level (de Wit et al., 2017; du Plessis et al., 2017; Kirwan et al., 2017; Lowe et al., 2016; Sacristan et al., 2016; Stegemann et al., 2016).

Furthermore, PHARMA's 50-year-old business model, based on scientific innovation and physician preferences, would have to be radically redesigned to accommodate the concept of PE in medicine development, with fundamental changes in culture, strategy and processes required to follow the new patient-centric PE approach (Blasimme & Vayena, 2016; Boudes et al., 2018; Dewulf, 2015; Eyeforpharma, 2017a; M. Y. Smith et al., 2016). The need for a patient-centric culture as an antecedent for the concept of PE in medicine development at the PHARMA level was further substantiated by 41 sources with 63 references from the thematic analysis of the literature (see ***Figure 7.2***).

(ii) <u>PE guidance and incentives</u> - an antecedent of PE in medicine development at the PHARMA level

While the majority of PHARMA acknowledged the potential positive outcomes associated with PE in medicine development, issues around how an effective, meaningful and feasible PE could be implemented in medicine development, within the ethical, social, legal (ESL) and regulatory framework, were heavily debated in the literature (de Wit et al., 2017; Lowe et al., 2016; H. Wilson et al., 2018). In a recent white paper, DIA (2017) argued the importance of balancing the benefits and risks assessment (BRA) of a medicine both from the technical, scientific perspective and, in terms of social value judgements, from the patient's perspective, which was not yet established within the current regulatory framework for the evaluation and approval of a new medicine. Developing a master framework to systematically integrate patient input into the medicine BRA produced by regulatory

authorities and health technology assessment (HTA) agencies was deemed necessary to offer the PE guidance and incentives for PHARMA to actively pursue PE in medicine development (Duffett, 2017; Eyeforpharma, 2017a; Frank et al., 2015).

Furthermore, there was still resistance from PHARMA to interacting directly with patients under the current ESL regulations, due to concerns relating to the perceived risks of the potential violation of data privacy, intellectual property, conflict of interests and pre-approval promotion associated with PE activities in medicine development (Adams & Petersen, 2016; Akhmetov & Bubnov, 2017; Hoos et al., 2015). A wide range of literature observed the need to develop a master ESL and methodological framework as a foundation to guide PHARMA in PE activities throughout the medicine development life-cycle (Bloom et al., 2018; Burns et al., 2014; CTTI, 2018; Dewulf, 2015; du Plessis et al., 2017; Frank et al., 2015; Kirwan et al., 2017; Martin-Kerry et al., 2017; Pushparajah, 2018; S. K. Smith et al., 2015). As a result, PE guidance and incentives were recognized as an antecedent for the concept of PE in medicine development at the PHARMA level by 21 sources with 33 references in the thematic analysis of the literature (see ***Figure 7.2***).

(iii) <u>Recognize the value of PE</u> - an antecedent of PE in medicine development at the PHARMA level

Given that the PE phenomenon is a new challenge for the pharmaceutical industry (PHARMA), where systematic integration of patient value into medicine development processes has not yet been established, several scholars suggested designing new PE processes, drawing on the value co-creation (VCC) theory to generate mutual benefits for patients and PHARMA (Akhmetov & Bubnov, 2017; Batalden et al., 2016; Croft & McLoughlin, 2015). For instance, du Plessis et al. (2017) argued that, as patients are more knowledgeable and empowered than ever before, patient experiences should be captured as key assets and resources to inform medicine development. Within this context, PE would

provide benefits at various stages of the medicine development process, including (i) identifying an unmet medical need and establishing a research agenda; (ii) designing the target product profile (TPP) and target population profile; (iii) informing and optimising the clinical trial design; (iv) improving outcomes through enhanced patient adherence; and (v) informing future research priorities (du Plessis et al., 2017). However, the integration of patient value into the medicine development processes was considered a substantial change which demands thorough assessment in terms of how to co-create value for both patients and PHARMA to generate mutual benefits, and this was not yet fully understood and recognized by PHARMA (Bloom et al., 2018; Duffett, 2017; Yeoman et al., 2016).

Croft and McLoughlin (2015) argued in a white paper that PHARMA has claimed patient centricity and PE in its mission statement for many years, with no link, however, to its business metrics or commercial benefits. It has been suggested that PE in medicine development be designed linked to the triple aims of PHARMA (i.e. creating patient value, driving scientific innovation and generating financial ROI) to support PHARMA in recognizing the value of PE in medicine development at the PHARMA level (Deloitte, 2016; Eyeforpharma, 2017a; Saarijarvi et al., 2013).

Taking the above discussions into account, recognizing the value of PE in the context of medicine development by PHARMA was suggested as a prerequisite for the genuine introduction of meaningful PE activities to medicine development (Batalden et al., 2016; Croft & McLoughlin, 2015; du Plessis et al., 2017; Getz, 2015; Levitan et al., 2018). Therefore, recognizing the value of PE was suggested as a key antecedent of PE in medicine development at the PHARMA level (supported by 20 sources with 48 references in a thematic analysis of the literature) (see ***Figure 7.2***).

4.2.3.3 Consequences of PE in medicine development at the PHARMA level

The following consequences of the concept of PE in medicine development at the PHARMA level were identified from the thematic analysis of the literature: (i) improved patient value and healthcare value through PE in medicine development (Blasimme & Vayena, 2016; Crawford et al., 2017; Israilov & Cho, 2017; Kirwan et al., 2017); (ii) improved innovation and business success by addressing unmet needs and achieving financial return on investment (ROI) (S. Davis et al., 2016; Domecq et al., 2014; Levitan et al., 2018; Stegemann et al., 2016); and (iii) improved reputation and trust through better process quality in terms of relevance, transparency, credibility and responsiveness (Burns et al., 2014; Deverka et al., 2012; Miseta, 2015b; Sharma, 2015). These expected positive consequences associated with PE in medicine development was supposed to lead to *improved business value* as an overarching core consequence at the PHARMA level collectively (supported by 64 sources with 168 references in a thematic analysis of the literature) (see ***Figure 7.3***). These identified consequences of PE in medicine development at the PHARMA level are further elaborated and justified in the following paragraphs.

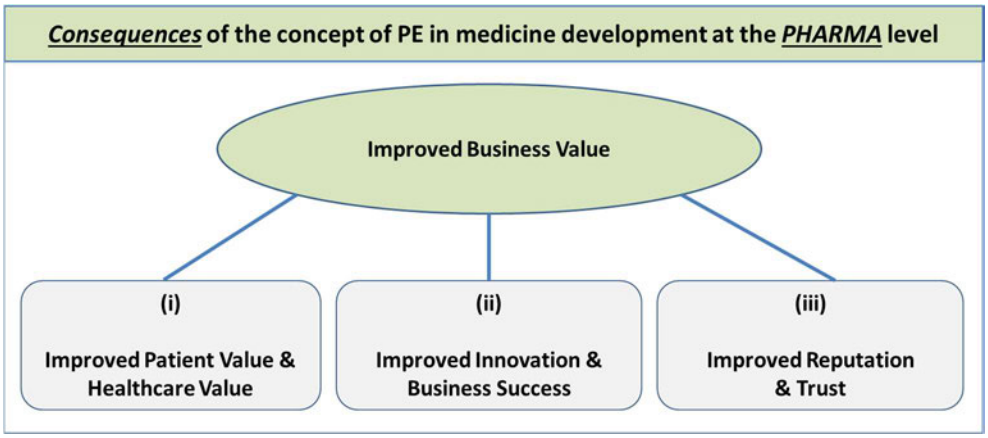

***Figure 7.3**: Consequences of PE in medicine development at the PHARMA level*

(i) <u>Improved patient value and healthcare value</u> - a consequence of PE in medicine development at the PHARMA level

Patient engagement (PE) was suggested to be inherently associated with the notion that patients have experiential knowledge of living with a condition, which is a valuable resource that should be harvested to inform the development of better medicines, thus delivering improved patient value and healthcare value (Blasimme & Vayena, 2016; Brett et al., 2014). Crawford et al. (2017) reported in an empirical study that the more medicine developers understand the patient value within PE in medicine development, the more effectively and efficiently they can develop better medicines for patients, thus improving patient value and healthcare value. Another empirical study by Kirwan et al. (2017) confirmed that patients' experiential knowledge of the disease burden added value to research knowledge, helping PHARMA to deliver improved patient value and healthcare value through PE in medicine development. Additionally, an empirical study by Messina and Grainger (2012), based on interviews with HTA agents (n=39) indicated that PHARMA has a major role to play in incorporating the patient experience into the medicine development process to co-create value for patients and healthcare.

Furthermore, a global empirical study on PE in medicine development (the *PARADIGM* project) conducted by IMI (2018) demonstrated that PE in medicine development delivered mutual benefits to both patients and PHARMA in terms of better health outcomes, co-creation and the dissemination of research results and knowledge. Similarly, a systematic literature review by Israilov and Cho (2017) suggested that co-creation with patients within PE in medicine development promoted peer learning and improved outcomes through the lens of quality management. The positive consequences associated with PE in medicine development described above align with the claims from the empirical study of Dewulf (2014):

> 'In any economic system that allows for choice, those providers who deliver the best customer experience across both dimensions (i.e., result and journey to this result) will survive and thrive; those who do not will simply disappear over time. … This is not different in health care. … All providers need to understand deeply what it means to be a patient and experience the solutions offered and the use of these insights to design solutions that better fit patients' needs.' (p. 10)

Consequently, PE has been seen as an essential approach to support PHARMA in delivering improved patient value and healthcare value as consequences of PE in medicine development (Boudes et al., 2018; Lowe et al., 2016; Marzorati & Pravettoni, 2017; Perfetto et al., 2017), which was further supported by 37 sources with 78 references from the thematic analysis of the literature in the present study (see ***Figure 7.3***).

(ii) <u>Improved innovation and business success</u> - a consequence of PE in medicine development at the PHARMA level

In the context of an increasingly value-based healthcare system with the trend moving towards patient-centred medicines, Stegemann et al. (2016) argued in a white paper that PE in medicine development allows PHARMA to identify the specific needs of the individual patient and/or distinct patient populations, thus providing the key drivers for PHARMA to design innovative medicines and healthcare solutions. In addition to the qualitative benefits associated with PE in medicine development in improved adherence, reduced disease burden, increased quality of life and reduction in medication errors, as demonstrated by several empirical studies (Bloom et al., 2018; Crawford et al., 2017; CUTTINGEDGE, 2016; Domecq et al., 2014), another empirical study from Levitan et al. (2018) offered evidence that effective PE in clinical trials could bring financial benefits in

terms of ROI for PHARMA. Similarly, Croft and McLoughlin (2015) argued in a white paper that it seems taboo for PHARMA to link patient value with financial ROI; however, PHARMA needs to balance its investment to address its triple aim of innovation, addressing unmet medical needs to create value for patients, and gaining financial ROI. In this regard, effective PE in medicine development could be a powerful means to help PHARMA to achieve this triple aim, gain strategic advantages and maintain business success (S. Davis et al., 2016; Deloitte, 2016; Getz, 2015; Levitan et al., 2018). Insightfully, a PHARMA executive commented in an interview conducted by Eyeforpharma (2015, p. 7) that 'the biggest misconception of PHARMA's business model is that what's right for the patient and what's right for the shareholder are fundamentally at odds; in fact, the reverse is true. When the patients' needs are our primary priority, business flourishes'.

Drawing on the above discussions, PE in medicine development could support PHARMA in aligning product offerings with patient need, leveraging the experiential knowledge of patients as a valuable resource to co-create innovative solutions, delivering positive patient health outcomes and, thereby, generating a competitive advantage and sustainable business success (Croft & McLoughlin, 2015; Devasirvatham, 2012; Dewulf, 2015; Levitan et al., 2018). As a result, improved innovation and business success - as a consequence of PE in medicine development at the PHARMA level - was supported further by 30 sources with 56 references from a thematic analysis of the literature (see ***Figure 7.3***).

(iii) <u>Improved reputation and trust</u> - a consequence of PE in medicine development at the PHARMA level

An empirical study by Miseta (2015b) indicated that there existed a mistrust of PHARMA on the part of patients, due to the conventional practice of treating patients as subjects rather than partners in the context of medicine development. PE was suggested in multiple studies to have improved the quality of interactions between PHARMA and patients

in terms of the improved trust, transparency, reciprocal respect and partnership, co-learning and knowledge-sharing, accountability and credibility, inclusiveness and responsiveness, legitimacy and fairness, competence and mutual benefits (Burns et al., 2014; Deverka et al., 2012; Miseta, 2015a; Sharma, 2015). Deverka et al. (2012) reported in a literature review that effective PE in medicine development would have a positive impact on process quality, of equal importance to the positive, tangible PE outcomes that will support PHARMA to improve its reputation and trust in the long term. Building trust was suggested to be the foundation for PHARMA to rebuild its reputation and form trusted partnerships with patients, and effective PE in medicine development would play a vital role in this regard (du Plessis et al., 2017; S. K. Smith et al., 2015).

Furthermore, several studies demonstrated that PE in medicine development could contribute to improved (i) relevance: patients' knowledge, perspectives and experience facilitate ethical deliberation and increase the relevance of the research (DIA, 2016); (ii) legitimacy and fairness: PE allows patients equal participation and access to knowledge, enabling them to make an effective contribution (EUPATI, 2016c); (iii) competence and mutual benefits: PE facilitates co-learning and knowledge-sharing which enhances competence building for both patients and PHARMA and generates mutual benefits (Frank et al., 2015); (iv) inclusiveness and responsiveness: the diversity of the patient population and perspectives are acknowledged and incorporated in the research process (Getz, 2015); and (v) credibility and trust: PE potentially leads to improved credibility and trust in the research results through better understanding of the patient perspective and experience (Deverka et al., 2012; Dewulf, 2015; Domecq et al., 2014; Holm et al., 2016).

As a result, *improved business value* - as an overarching key consequence of PE in medicine development at the PHARMA level - was supported by 24 sources with 33 references from the thematic analysis of the literature data (see ***Figure 7.3***).

4.2.4 Summary

The concept of PE in medicine development at the PHARMA level (see ***Figure 7***) was heavily affected by the advancement of this concept both at the society level (see ***Figure 5***) which has influenced PHARMA's business strategy and operations through social norms, policy and regulations, and at the patient level (see ***Figure 6***), as these are becoming increasingly empowered and engaged in medicine develop. Taking into consideration that PHARMA needs to serve both patients (creating patient value with innovative medicines) and society (creating healthcare value though addressing unmet medical needs with improved healthcare outcomes), the meanings of PE in medicine development at both patient and societal levels are highly relevant for PHARMA in designing an effective PE strategy to meet the expectations of its customers – both patients and society. PE in medicine development would, consequently, lead to financial benefits and maintaining sustainable business value at the PHARMA level. Drawing on the in-depth discussions and comprehensive evidence offered in the above sections, a provisional thematic map regarding the concept of PE in medicine development was produced (see ***Figure 8*)**, developed through the thematic analysis of the literature data in the present study (as discussed above).

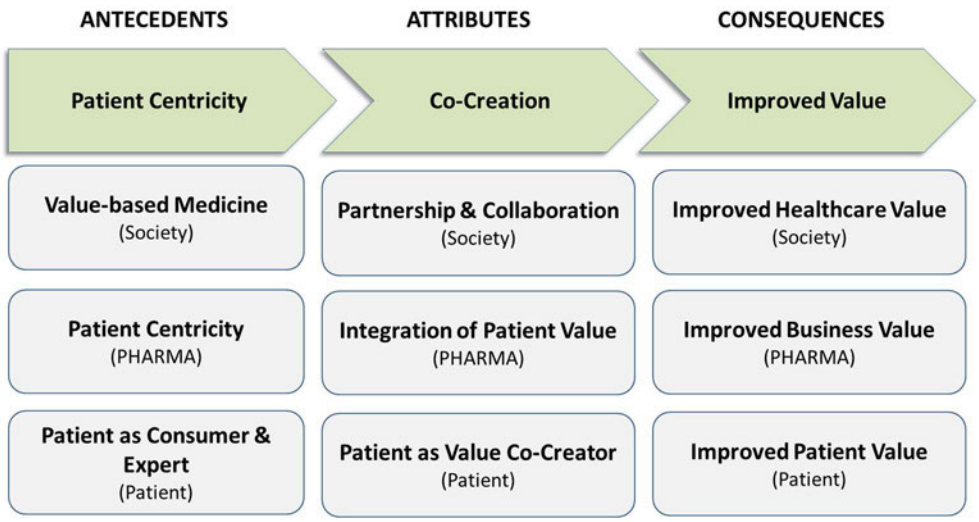

Figure 8*: Thematic map of PE in medicine development developed from the theoretical phase*

The provisional thematic map regarding the concept of PE in medicine development (see ***Figure 8***) suggests that *patient centricity*, as an overarching key antecedent for the concept of PE in medicine development, is driven by the paradigm shift to VBM at the societal level, the patient as consumer and expert at the patient level, and increased patient-centricity at the PHARMA level. These provisional claims are intricately linked with the initial theoretical perspectives based on VBM, VCC and SDL, which are inherently customer-centric (or patient-centric) (as discussed in Section 2.5).

Next, *co-creation*, identified as an essential defining attribute of the concept of PE in medicine development, shows a direct link with the theoretical core from a VCC and SDL perspective as defined for the present study, which contend that customers are always value co-creators (as discussed in Section 2.5). As an overarching defining attribute of PE in medicine development, co-creation is supported by the themes of the patient as value co-creator at the patient level, partnership and collaboration at the society level, and integration of patient value at the PHARMA level (see ***Figure 8***).

Lastly, PE in medicine development is expected to contribute to *improved value* as an overarching key consequence in terms of improved patient value for patients, improved healthcare value for society and improved business value for PHARMA, in line with the theoretical propositions of VBM, VCC and SDL, which state that customer (or patient) engagement allows value co-creation for the customer's fulfilment of value through interactions between the firm and customers, and value is determined by customers (i.e. patients in the context of PE in medicine development) as the beneficiary, which will generate mutual benefits for all involved actors (as discussed in Section 2.5).

The provisional thematic map of PE in medicine development developed from the theoretical phase (***Figure 8***) is carried over and corroborated with the empirical data gathered from the fieldwork (see Chapter 5). Together they inform the development of a final PE

conceptual framework and theoretical propositions in medicine development from a value-creation perspective, which is presented and justified further in Chapter 6.

4.3 Barriers to and facilitators for the concept of PE in medicine development

To further explore the concept of PE in medicine development and address RO1 (see Section 1.2), the influencing factors associated with the PE phenomenon in medicine development, in terms of barriers, facilitators, were analysed based on inductive coding and thematic analysis of the literature. The influencing factors identified offered contextual information about PE in medicine development which are highly relevant for a comprehensive understanding of the concept of PE and its current use in medicine development practice. The identified barriers and facilitators related to PE in medicine development, derived from the thematic analysis of literature, are presented in ***Table 7***. In-depth discussion is provided in the following sections, which are organized and presented at the level of society, patient, and PHARMA, respectively.

Table 7: *Barriers to and facilitators for PE in medicine development developed from the theoretical phase*

	BARRIERS	FACILITATORS
SOCIETY [section 4.3.1]	i. Discrepancy of VALUE perspective ii. Cultual resistance to change iii. Ethical, Social, Legal (ESL) constraints iv. Lack of incentives and evidence of PE benefits	i. PE Framework & Platform based on aligned VALUE ii. Define ESL framework for PE iii. Incentives for PE – align reimbursement with patient value iv. Create evidence base for PE
PHARMA [section 4.3.3]	i. Culture resistance & tokenism ii. How – methodology challenges iii. Ethical, Social, Legal (ESL) constraints iv. Lack of evidence of ROI of PE	i. Culture change & Process Design ii. Aligned PE Framework & Platform endorsed by all HC stakeholders iii. Define PE measurements & generate evidence of PE outcome
PATIENT [section 4.3.2]	i. Health literacy & Capacity ii. How - the right patients & patient inputs iii. Organisation & compensation	i. Education & Traning to support Patient Experts in PE ii. Define methodology of how to incoporate patient inputs via PE iii. Enhance PE through collaboration with Patient Organisations

4.3.1 Factors influencing PE in medicine development at the societal level

The following key barriers to the concept of PE in medicine development at the societal level were identified from the thematic analysis of literature: (i) discrepancy of value perspectives among healthcare stakeholders (Armstrong & Bloom, 2017; Bae, 2015; Kelly et al., 2015); (ii) cultural resistance to change (Laurance et al., 2014; Sacristan et al., 2016; S. K. Smith et al., 2015); (iii) perceived ethical, social and legal (ESL) constraints (Adams & Petersen, 2016; Akhmetov & Bubnov, 2017; Burns et al., 2014); and (iv) lack of incentives and evidence for PE benefits (Kendell et al., 2014; Kohler et al., 2017; Lamberti & Awatin, 2017) (see ***Table 7***). These identified barriers to the concept of PE in medicine development at the society level are further elaborated upon and interpreted below.

(i) <u>Discrepancy of value perspectives</u> - a barrier to PE in medicine development at the society level

Bae (2015) argued in his theoretical research that although patient value has been prioritized in healthcare settings since the beginning of the twenty-first century, different value perspectives are still followed by the various healthcare stakeholders involved (i.e., HAs, HTA agents, PHARMA, and patients). Within a VBM paradigm, value needs to be made explicit and integrated into the decision-making of healthcare stakeholders to realize the potential benefits of PE (Kelly et al., 2015). However, as Kelly et al. observe:

> 'Values are about the world as it ought to be; … Different people will have different values, and it is very hard to resolve value-based disagreement on the basis of scientific evidence; … Different values underpin different priorities and different kinds of ethical judgements.' (Kelly et al., 2015, p. 2)

Conventionally, healthcare professionals (including PHARMA, HA and HTA agents) considered the value of medical treatment predominantly based on scientific evidence, drawing on an evidence-based medicine (EBM) value-evaluation system (Marzorati & Pravettoni, 2017). In contrast, from a patient perspective, robust scientific evidence 'is meaningless unless societal, cultural, and political perspectives are taken into account – since such value-based influences necessarily frame the problem and shape the research questions and the interpretation of findings' (Kelly et al., 2015, p. 3). For instance, measurement of the efficacy and safety of a medicinal product through rigid clinical trials are still considered robust scientific evidence to meet gold standards in medicine development by PHARMA, HA and HTA (Miller et al., 2017). However, disease burden is not limited to disease status; the perceived value associated with a medical treatment from a patient's perspective is much broader and goes beyond clinical dimensions (du Plessis et al., 2017). Therefore, additional value elements such as psycho-social, emotional and cognitive functioning, as well as the quality of healthcare delivery in terms of communication, interactions and shared decision-making, play equally significant roles in patients' perception of patient value and healthcare value (Kelly et al., 2015; Marzorati & Pravettoni, 2017; Miller et al., 2017).

The tension between these various value perspectives is likely to cause conflict, so that PE in medicine development may not always be the priority for each stakeholder. Additionally, patients may propose different and diverse values, and these may also change over time, making value judgements even more complex within PE in medicine development (Bae, 2015; Kelly et al., 2015). Various studies observed that the discrepancy in value perspectives among healthcare stakeholders is a key hurdle for establishing meaningful PE to pursue VBM in medicine development (Boudes et al., 2018; Gallivan et al., 2012; Marzorati & Pravettoni, 2017; Mitchell et al., 2017; Perfetto et al., 2017; Pushparajah, 2018;

M. Y. Smith et al., 2016), as supported further by 27 sources with 37 references through the thematic analysis of the literature in the present study (see ***Annex 8***).

To overcome this barrier to PE in medicine development, it was considered urgently necessary to develop a master PE framework with a set of aligned value parameters and methodology allowing the incorporation of different value perspectives, which could facilitate PE in medicine development in practice (Boudes et al., 2018; Brett et al., 2012; Lamberti & Awatin, 2017). This was identified as a key facilitator to PE in medicine development at the societal level from the thematic analysis of literature (see ***Table 7***).

(ii) <u>Cultural resistance to change</u> - a barrier to PE in medicine development at the societal level

The following factors in cultural resistance to PE in medicine development at the societal level were identified through the thematic analysis of the literature: (i) physician autonomy and resistance to lay involvement (Armstrong & Bloom, 2017); (ii) patients' feeling overwhelmed by medical terminology and scientific methods (Carroll et al., 2017); (iii) the imbalance of power between healthcare professionals (HCP) and patients (Israilov & Cho, 2017); and (iv) the high methodological hurdle set by regulators for patient-reported outcomes (PRO) in clinical studies (Basch, 2013).

In an empirical study based on interviews with healthcare stakeholders (n=32), Bloom et al. (2018) argued that this cultural resistance to the new PE phenomenon is related to the mismatched expectations and priorities among healthcare stakeholders, the perceived wishful thinking of patient participants, and the lack of value justification for PE in medicine development in relation to the time and resources involved. Following an online survey with 755 physicians and 1255 nurses, Getz (2015) argued that the increased complexity and methodological difficulty in incorporating diverse patient views into the well-established, scientific, medicine-development processes are the major reasons for HCP's reluctance to

engage with the concept of PE in medicine development. As a result, cultural resistance to change as a key barrier to the concept of PE in medicine development at the society level was further substantiated by 21 sources with 28 references through a thematic analysis of the literature (see ***Table 7***).

(iii) <u>Ethical, social, and legal (ESL) constraints</u> - a barrier to PE in medicine development at the society level

Ethical, social and legal (ESL) issues concerning data privacy and conflict of interests were often cited in the literature as a major barrier for HCPs in adopting the PE approach, but were also considered instrumental in providing a safe harbour to facilitate a trustful PE in medicine development (Adams & Petersen, 2016; Pushparajah, 2018). A regulatory perspective regarding what constitutes appropriate PE in medicine development, and what actions may be seen as violating certain regulations governing pre-approval promotions, was not clearly defined and this regulatory uncertainty may prevent HCPs (including PHARMA) from actively pursuing a PE approach in medicine development (Akhmetov & Bubnov, 2017; NHC, 2015a).

Studies indicated that both PHARMA (Perfetto & Oehrlein, 2015) and patient organisations (Sienkiewicz & van Lingen, 2017) sought regulatory guidance to overcome these barriers to PE in medicine development. The majority of the regulatory efforts were described as still in the pilot stage and a well-defined ESL guidance and compliance framework, addressing potential methodological, legal and ethical concerns, was considered fundamental for the adoption of the concept of PE in medicine development (Burns et al., 2014; Crawford et al., 2017; Dewulf, 2015; Hoos et al., 2015; M. Y. Smith et al., 2016; von Tigerstrom, 2016). Furthermore, the current ESL guidance was seen as not sufficient to support a more widespread adoption of the concept of PE in medicine development (Perfetto

& Oehrlein, 2015; Lamberti & Awatin, 2017; NHC, 2015a), as supported by 18 sources with 23 references through the thematic analysis of the literature (see ***Table 7***).

(iv) <u>Lack of incentives and evidence for PE benefits</u> - a barrier to PE in medicine development at the society level

Porter (2010) contended that, in a VBM paradigm with patient value at the core and as the overarching goal of all healthcare stakeholders, value creation for patients should determine the rewards for all healthcare actors involved. Following this line of thinking, PE in medicine development was expected to deliver value for patients and rewards to those healthcare actors who have adopted the PE approach (Basch, 2013; Batalden et al., 2016). However, current literature indicated little evidence demonstrating the effectiveness and beneficial outcomes of the concept of PE in this context (Bloom et al., 2018; Boudes et al., 2018). The lack of evidence may be due in part to the absence of a thorough understanding of the concept of PE in medicine development itself (i.e. what does PE mean, and how to do PE), and in part to the operational difficulty of establishing an evidence base to support the outcomes of PE initiatives (Gallivan et al., 2012; Kendell et al., 2014; Kohler et al., 2017). Furthermore, tangible incentives from both regulatory approval and market access, linked with PE activities in medicine development, were deemed necessary to justify the investment of PE in medicine development, given the considerable resources and efforts involved (Basch, 2017; Burns et al., 2014; Carroll et al., 2017; CTTI, 2018; Perfetto & Oehrlein, 2015; Pushparajah, 2018). As a result, lack of incentives or evidence for PE benefits was seen as a critical barrier to PE in medicine development at the societal level, which was further substantiated by 36 sources with 70 references through the TA of the literature (***Table 7***).

Corresponding to these major barriers to the concept of PE in medicine development, as identified at the society level and discussed above, the following facilitators which may positively advance the concept of PE in medicine development at the society level by

overcoming these barriers were identified from the literature analysis: (i) development of a PE framework and platform based on aligned value (Boutin et al., 2017; DIA, 2017; Lamberti & Awatin, 2017; Lowe et al., 2016); (ii) development of an ESL framework and guidance for safe and meaningful PE (Dewulf, 2015; Laurance et al., 2014; M. Y. Smith et al., 2016); (iii) creation of incentives for PE activities through aligning regulatory approval and reimbursement policy with patient value (Akhmetov & Bubnov, 2017; DIA, 2016; Perfetto et al., 2017); and (iv) creation of an evidence base to demonstrate the associated benefits of PE in medicine development (Chiauzzi et al., 2016; Kohler et al., 2017; Levitan et al., 2018; Pushparajah, 2018; S. K. Smith et al., 2015) (see ***Table 7***).

Furthermore, in-depth thematic analysis of the literature allowed the identification of key influencing factors of the concept of PE in medicine development at the society level as follows (see ***Table 7.1***):

(a) The discrepancy of value perspectives of healthcare stakeholders was suggested as the key barrier to PE in medicine development at the society level (supported by 62 sources with 158 references through the thematic analysis of the literature); and

(b) The development of a PE conceptual framework with aligned value endorsed by all healthcare stakeholders was identified as a key facilitator to overcome the key barrier (supported by 30 sources with 69 references through the thematic analysis of literature).

Table 7.1*: Key factors influencing PE in medicine development at the society level*

	KEY BARRIER	KEY FACILITATOR
SOCIETY [section 4.3.1]	**Discrepancy of value perspectives of healthcare stakeholders** (supported by 62 sources with 158 references)	**Development of PE conceptual framework with aligned value endorsed by all healthcare stakeholders** (supported by 30 sources with 69 references)

Several studies observed that the value perspectives associated with PE in medicine development differ between healthcare stakeholders – with HCPs (including PHARMA, HA, and HTA) focussing on the scientific evidence (i.e., efficacy and safety of a medicinal product), while patients emphasize a broader health-related quality of life (HrQoL) perspective (Armstrong & Bloom, 2017; Bae, 2015; Kelly et al., 2015; Mitchell et al., 2017). Although the question of why patients' perspectives are important in medicine development was largely answered and accepted by all healthcare stakeholders, the question of how to incorporate patient value into medicine development within PE remains to be answered, and a solution was suggested to be urgently needed to facilitate the adoption of PE in medicine development practice (Lamberti & Awatin, 2017; NHC, 2015; Perfetto et al., 2015; Smith et al., 2016). Accordingly, the RO3 in the present study aims to address these research issues through development of a PE conceptual framework in medicine development with aligned value understanding from a VCC perspective (see Section 6.3).

4.3.2 Factors influencing PE in medicine development at the patient level

Thematic analysis of literature identified the following major barriers to the concept of PE in medicine development at the patient level: (i) health literacy and capacity (Armstrong & Bloom, 2017; Berger et al., 2014; Brett et al., 2014); (ii) methodology challenges about how to engage the right patients to obtain the right inputs (Sienkiewicz & van Lingen, 2017; Tapp et al., 2017; von Tigerstrom, 2016); and (iii) organisation and compensation issues related to PE initiatives (Bright et al., 2015; EPF, 2013; Sheridan et al., 2015) (see ***Table 7***). These identified barriers to the concept of PE in medicine development at the patient level are discussed further below.

(i) Health literacy and capacity - a barrier to PE in medicine development at the patient level

Health literacy was defined as 'people's ability to obtain, process, communicate, and understand basic health information and services', and was considered as an essential facilitator for patients to participate effectively in PE activities (Koh et al., 2013, p. 1). Studies revealed that the primary cause of scepticism towards the concept of PE in medicine development was the concern that patients do not have appropriate medical training and the necessary knowledge to contribute to medicine development activities (Armstrong, Rueda, et al., 2017). Furthermore, the medical terminology used in medicine development was suggested as an additional barrier to meaningful PE for patients in this context (Getz, 2017; M. Y. Smith et al., 2016).

It was further argued that the limited health literacy of patients represents a system issue, not merely an issue at the level of the individual patient (Dubois et al., 2016; Koh et al., 2013). In an empirical study based on an online survey with more than 2,000 physicians and nurses, Getz (2017) demonstrated that limited health literacy and capacity was the major barrier preventing patients from active participation in clinical trials. Similar claims were made by Lowe et al. (2016) in an empirical study with healthcare leaders which found that patients' ability to participate in medicine development was challenged due to a perceived lack of medical knowledge. The severity of illness and a self-perceived subordinate attitude were suggested as additional barriers impeding patients' active engagement in medicine development by Berger et al. (2014). A recent empirical study by Bloom et al. (2018) offered further evidence that a perceived lack of scientific understanding, and wishful thinking on the part of patients, were considered major hurdles for meaningful PE in medicine development at the patient level, as substantiated by 14 sources with 28 references through the thematic analysis of the literature (see ***Table 7***).

(ii) <u>How - the right patients and patient inputs</u> - a barrier to PE in medicine development at the patient level

In an empirical study based on interviews with healthcare leaders, Lowe et al. (2016) discussed how patients may not be capable of representing experiences beyond their own, and that their input was therefore considered biased or not objective. Furthermore, contextual factors, such as culture, religion, social-economic status, may impede the participation of certain patient populations in PE activities in medicine development (M. Y. Smith et al., 2016; Tapp et al., 2017). The challenges concerning the generalizability of individual patient's experiences and/or those of a small group of individuals were repeatedly discussed in the literature as a major methodological barrier for the adoption of PE in medicine development at the patient level (Carroll et al., 2017; Perfetto & Oehrlein, 2015; NHC, 2015a; Sienkiewicz & van Lingen, 2017).

Another issue related to the patient's role within PE in medicine development was described by von Tigerstrom (2016) as the multiplicity of roles that patients may play in PE processes - as patients, advocates, citizens, taxpayers, lay users, consumers and stakeholders. Different perspectives may, thus, be adopted by patients based on different assumed roles and these may change over time, challenging the validity of the input data collected from patients over time. Similarly, Perfetto and Oehrlein (2015) argued in an empirical study that patients' experiences could be heterogeneous and may change over time as personal circumstances and/or the disease state changes. Therefore, developing proper methods for gathering the right inputs from the right patient population was deemed as a critical factor in enabling effective PE in medicine development, as further supported by 12 sources with 38 references from the thematic analysis of the literature (see ***Table 7***).

(iii) <u>Organisation and compensation challenges</u> - a barrier to PE in medicine development at the patient level

Logistical challenges, inadequate compensation and costly endeavours in terms of time and resources invested in patient involvement in PE activities were often reported as a key barrier to PE in medicine development at the patient level (Sheridan et al., 2015; Sienkiewicz & van Lingen, 2017; Tapp et al., 2017). With the increasing demand to systematically gather patient input and advance the concept of PE in medicine development, patient organisations (POs) became important emerging patient intermediaries, able to facilitate relationships with the wider patient community (CTTI, 2018), represent the collective view of a specific patient population suffering from a certain disease (DIA, 2017), and introduce disease-specific expertise and experience to the interactions with wider healthcare stakeholders (EMA, 2016a; FDA, 2018a).

Furthermore, Hoos et al. (2015) argued that effective PE requires the skills of expert patients (i.e. those who have obtained a technical understanding of medicine development processes through training and/or experience, in addition to their disease-specific expertise) and adequate expertise which could be built up through patient networks and POs. Accordingly, appropriate funding and resource support for PE-related education and PO training activities were deemed necessary to overcome the operational barriers to the concept of PE at the level of the patient (DIA, 2016; EPF, 2013; EUPATI, 2016c; NHC, 2015a; Sienkiewicz & van Lingen, 2017). This barrier to PE in medicine development at the patient level was further supported by 11 sources with 11 references from the thematic analysis of the literature (see ***Table 7***).

Corresponding to the barriers identified to the concept of PE in medicine development at the patient level (as discussed in the above paragraphs), the following facilitators to overcome these barriers were identified from the literature analysis: (i)

education, training, and support for patients to enable effective PE participation (Bright et al., 2015; Gruman et al., 2010; NHC, 2016; Pushparajah, 2018); (ii) a defined methodology for incorporating patient input through PE activities (Arkind et al., 2015; Carroll et al., 2017; Duffett, 2017; Kirwan et al., 2017); and (iii) collaboration with POs to enhance effective PE (Bloom et al., 2018; Holm et al., 2016; Hoos et al., 2015; Kirwan et al., 2017) (see ***Table 7***).

A further, in-depth, thematic analysis of the literature found the following key factors influencing PE in medicine development at the patient level (see ***Table 7.2***):

(a) methodology challenges to engaging the right patients with the right inputs as a key barrier (supported by 25 sources with 77 references); and

(b) development of an aligned methodology to incorporate meaningful patient inputs as a key facilitator (supported by 31 sources with 56 references).

Table 7.2: *Key factors influencing PE in medicine development at the patient level*

	KEY BARRIER	KEY FACILITATOR
PATIENT [section 4.3.2]	**Methodology challenges to engage the right patients with the right inputs** (supported by 25 sources with 77 references)	**Development of aligned methodology to incorporate meaningful patients' inputs** (supported by 31 sources with 56 references)

Barello et al. (2014, p. 12) explained the PE methodology challenge as a key barrier to PE in medicine development at the patient level by stating that 'the understanding of patients' subjective experience is often reduced to its cognitive, behaviour or emotional components, whereas a holistic understanding of the patients' complex psycho-social experience is lacking', although PE in medicine development was expected to 'incorporate patients' perceptions, values and preferences, thus making health care truly responsive to patients' subjective needs'. Perfetto et al. (2015, p.1) confirmed this view: 'it's difficult for a single or small group of individuals to faithfully represent the patients' perspectives as a

whole'. The development of a science-based method to gather valid and faithful patient input was, therefore, indicated as a key facilitator for meaningful PE in medicine development at the patient level (Birnbaum et al., 2015; Carroll et al., 2017; Tapp et al., 2017; von Tigerstrom, 2016) (see ***Table 7.2***).

The science of PE in medicine development is yet to develop a consensus-driven methodology framework for the meaningful incorporation of patient input into medicine development (Baines & de Bere, 2018; EPF, 2013; Miseta, 2015b). Currently, different stakeholder perspectives persist, based on various research paradigms: realism-based, natural-science research approaches are used by HCPs, while most PE experts use constructivism-based, social-science research paradigms (Armstrong et al., 2017; Bloom et al., 2018). A social constructivist ontological stance was considered more appropriate to develop a consensus-driven, PE-methodology framework, to allow the incorporation of different stakeholder perspectives including those of patients (CTTI, 2018; Kirwan et al., 2017; NHC, 2015). A PE conceptual framework in medicine development, developed from a social constructivist stance together with relevant healthcare stakeholders in the present study (RO3), therefore, offers a foundational work to achieve consensus understandings among stakeholders about the PE phenomenon in medicine development.

4.3.3 Factors influencing PE in medicine development at the PHARMA level

The thematic analysis of the literature in the present study identified four major barriers to the concept of PE in medicine development at the PHARMA level: (i) culture resistance and tokenism (Hahn et al., 2017; Hall et al., 2018; Levitan et al., 2018; R. Robinson, 2013; M. Y. Smith et al., 2016); (ii) how - methodological challenges related to PE implementation (Bloom et al., 2018; Carroll et al., 2017; Mitchell et al., 2017; Pushparajah, 2018); (iii) ethical, social and legal (ESL) constraints associated with PE implementation (Birnbaum et al., 2015; Boutin et al., 2017; Croft & McLoughlin, 2015;

Wong-Rieger, 2016); and (iv) lack of evidence about the financial ROI of PE initiatives (Batalden et al., 2016; Bloom et al., 2018; Brett et al., 2014; Getz, 2015; Levitan et al., 2018) (see ***Table 7***). These barriers are elaborated and justified in the following paragraphs.

(i) <u>Culture resistance and tokenism</u> - a barrier to PE in medicine development at the PHARMA level

Levitan et al. (2018) argued in an empirical study that, despite a wide consensus on the moral and ethical imperative for PE in medicine development, HCPs (including PHARMA) were often reluctant to go beyond paying lip service to the principles of PE with no true effort to collaborate with patients. These symbolic efforts were repeatedly described as tokenism in empirical studies by Hahn et al. (2017) and Hall et al. (2018). The literature analysis revealed multiple factors behind this cultural resistance and tokenism, including scepticism about patients' capability to contribute to medicine development (Duffett, 2017); the lack of internal operational mechanisms for PE within PHARMA (Bloom et al., 2018); concerns about conflicts of interest and other legal constraints (Francer et al., 2014); and scepticism about the real benefits of PE initiatives (Levitan et al., 2018; Lowe et al., 2016).

Furthermore, empirical studies based on interviews with PHARMA executives revealed that the concept of PE would have the potential to disrupt the existing business model of PHARMA, which is used to performing medical research on, rather than with patients; still regarding patients as a source of data, not a true research partner (R. Robinson, 2013; Sacristan et al., 2016). Although some PHARMA were reported to have implemented change, to capture the potential advantages of this new concept of PE (Miseta, 2015a; Pushparajah, 2018; Yeoman et al., 2016), cultural resistance and tokenism were shown to persist in PHARMA, with significant effort needed to overcome these hurdles and introduce PE in medicine development (Bloom et al., 2018; Boudes et al., 2018; Boutin et al., 2017; Carroll et al., 2017; Crawford et al., 2017; Shippee et al., 2015; Sienkiewicz & van Lingen,

2017; M. Y. Smith et al., 2016). Further, culture resistance and tokenism as a barrier to the concept of PE in medicine development at the PHARMA level were supported by 32 sources with 56 references from the thematic analysis of the literature (see ***Table 7***).

(ii) How - methodological challenges - a barrier to PE in medicine development at the PHARMA level

Pushparajah (2018) reported that a major barrier to PE at the PHARMA level is the lack of a standardized methodology guiding how to incorporate patient perspectives into the medicine development process through PE. In particular, methodological challenges focussed on incorporating heterogeneous patient input into the well-established scientific methods regulated by HA and HTA agents (de Bekker-Grob et al., 2017). Although some high-level industry-wide methodological guidance related to PE in medicine development has been provided by regulators and industry associations (EFPIA, 2011; EMA, 2016b; FDA, 2018a, 2018b; PFMD, 2018b; PhRMA, 2016), the challenges associated with incorporating patient experiences (which are mostly in the form of individual qualitative data) into robust scientific evidence (which is predominantly in the form of population-based quantitative data rigorously scrutinized by regulators) throughout the medicine development processes were repeatedly reported as a key barrier to PE in medicine development at the PHARMA level (Bloom et al., 2018; Brett et al., 2014; Lowe et al., 2016; Mitchell et al., 2017).

Empirical studies from Carroll et al. (2017) and de Bekker-Grob et al. (2017) suggested an urgent need to develop aligned, scientifically valid methods to guide PE processes in capturing the patient perspective, through balancing the expectations of multiple stakeholders (such as regulators, HTA agents and reimbursement bodies) and feeding them into their existing decision-making processes. A key aspect in this regard was the integration of patients' voices into the benefits and risks assessment (BRA) throughout the medicine development processes, to form a multi-criteria medicine-evaluation framework

incorporating the perspectives of all healthcare stakeholders, including patients, through PE (DIA, 2015; du Plessis et al., 2017; EUPATI, 2016c; FDA, 2016; NASEM, 2018). As a result, the identification of methodological challenges as a key barrier to the concept of PE in medicine development at the PHARMA level was further supported by 27 sources with 51 references from the thematic analysis of the literature (see ***Table 7***).

(iii) <u>Ethical, social and legal (ESL) constraints</u> - a barrier to PE in medicine development at the PHARMA level

Ethical, social and legal (ESL) challenges associated with the concept of PE in medicine development were repeatedly discussed as a key challenge for PHARMA in the literature (Domecq et al., 2014; Lowe et al., 2016; NHC, 2016). PHARMA's interactions with patients and POs were strictly regulated by guidelines and industry codes (EFPIA, 2011; EMA, 2014; FDA, 2009; PhRMA, 2016), which were considered, however, insufficient to guide emerging PE activities in medicine development (Adams & Petersen, 2016; Francer et al., 2014; Pushparajah, 2018).

Various empirical studies conducted with PHARMA executives demonstrated that the perceived compliance risk associated with PE in medicine development (although non-promotional PE is possible in most if not all countries) and potential conflicts of interest were regarded as key barriers, preventing PHARMA from actively adopting PE in medicine development (Birnbaum et al., 2015; Croft & McLoughlin, 2015; du Plessis et al., 2017; Wong-Rieger, 2016). This was further supported by 13 sources with 21 references through the thematic analysis of the literature (see ***Table 7***).

(iv) <u>Lack of evidence for financial ROI of PE</u> - a barrier to PE in medicine development at the PHARMA level

In an empirical study based on interviews with healthcare practitioners, Bloom et al. (2018) argued that, considering the significant effort and time invested in PE activities by all participants, the lack of evidence regarding positive outcomes and financial ROI associated with PE initiatives was regarded as a key hurdle for the active adoption of PE by PHARMA in medicine development. Although potential benefits related to the concept of PE in medicine development were widely suggested in the literature, little empirical evidence was provided to substantiate these assumed positive outcomes (Boudes et al., 2018; Brett et al., 2010). A systematic review by Burns et al. (2014) reported that little research had been conducted to measure the outcomes of PE; thus, an evidence base supporting the benefits of PE in medicine development was missing in the current literature. However, a robust evidence base, including defined measurement metrics and quantified economic benefits (e.g. in terms of ROI) associated with PE initiatives, was deemed necessary to support the assumptions that PE in medicine development would improve patient value and healthcare value and, thus, enhance the business value of PHARMA (Carman & Workman, 2017; CUTTINGEDGE, 2016; Duffett, 2017).

Given that gaining financial ROI from PE activities is one of the triple aims of PHARMA (alongside delivering patient value and innovation for healthcare), in order to maintain competitiveness and sustainability, future research building an evidence base for PE initiatives in medicine development was repeatedly urged by scholars and practitioners in the current literature (CUTTINGEDGE, 2016; Eyeforpharma, 2017a; Getz, 2015; Gurtner & Soyez, 2016; Levitan et al., 2018). It was further supported by 32 sources with 57 references through the thematic analysis of the literature (see ***Table 7***).

Corresponding to the above discussed barriers to the concept of PE in medicine development at the PHARMA level, the following facilitating actions to overcome these hurdles and advance the concept of PE in medicine development were identified through the

literature analysis: (i) drive culture change and integrate PE into existing PHARMA operations (Baines & de Bere, 2018; Boutin et al., 2017; Collier, 2015; Laurance et al., 2014); (ii) develop an aligned PE framework and platform endorsed by all healthcare stakeholders (Batalden et al., 2016; Bloom et al., 2018; DIA, 2017; Sartori et al., 2016); and (iii) develop PE measurement metrics and generate an evidence base for the assumed positive outcomes related to PE initiatives (Burns et al., 2014; Croft & McLoughlin, 2015; CUTTINGEDGE, 2016; du Plessis et al., 2017; Getz, 2015; Kirwan et al., 2017; Levitan et al., 2018; Mitchell et al., 2017; Pushparajah, 2018) (see ***Table 7***).

Lastly, further in-depth thematic analysis of the literature concerning key influencing factors on PE in medicine development at the PHARMA level revealed (see ***Table 7.3***):

(a) methodology challenges to the integration of PE into established medicine development as a key barrier to PE in medicine development at the PHARMA level (supported by 53 sources with 186 references); and

(b) development of an aligned PE process framework endorsed by all healthcare stakeholders as a key facilitator (supported by 39 sources with 104 references).

Table 7.3: *Key factors influencing PE in medicine development at the PHARMA level*

	KEY BARRIER	KEY FACILITATOR
PHARMA [section 4.3.3]	**Methodology challenges to integrate PE into established medicine development** (supported by 53 sources with 186 references)	**Development of aligned PE process framework endorsed by all healthcare stakeholders** (supported by 39 sources with 104 references)

4.3.4 Summary

The thematic analysis of the literature in this section offered insights into the key influencing factors (both barriers and facilitators) regarding PE in medicine development at the level of society, the patient and PHARMA (summarized and presented in ***Table 7.4;*** for

details, see ***Annex 8***). This provided contextual information that may impact on the development and application of the concept of PE in medicine development in the practices. Consideration was given to understanding the key barriers that might prevent the effective application of PE in medicine development, and the key facilitators which may help overcome these barriers to advance the concept of PE in medicine development.

Table 7.4: *Summary of key influencing factors regarding PE in medicine development*

	KEY BARRIERS	KEY FACILITATORS
SOCIETY [section 4.3.1]	Discrepancy of value perspectives of healthcare stakeholders	Development of PE conceptual framework with aligned value endorsed by all healthcare stakeholders
PHARMA [section 4.3.3]	Methodology challenges to integrate PE into established medicine development	Development of aligned PE process framework endorsed by all healthcare stakeholders
PATIENT [section 4.3.2]	Methodology challenges to engage the right patients with the right inputs	Development of aligned methodology to incorporate meaningful patients' inputs

As illustrated in ***Table 7.4***, the methodological challenges associated with PE in medicine development were identified as a major block at both the patient and PHARMA levels, while the discrepancy in value perspectives between healthcare stakeholders was showed as a major barrier to PE in medicine development at the society level. Correspondingly, the development of a PE conceptual framework based on aligned value understanding at the society level, and the development of a PE methodology framework at the PHARMA and patient levels were suggested as key facilitators to PE in medicine development. These findings have both theoretical and practical implications for the further advancement of the concept of PE in the context of medicine development.

From a theoretical perspective, a PE conceptual framework based on aligned value understanding with healthcare stakeholders throughout the medicine development lifecycle was clearly shown to be a major knowledge gap (Boudes et al., 2018; Lamberti & Awatin, 2017; Lowe et al., 2016), but was also cited as the key facilitator needed to advance the concept of PE in medicine development (see discussions in this section). This provided further justification to develop a conceptual framework for PE in medicine development in the present study, based on the consensus understandings of different healthcare stakeholders (RO3). A conceptual framework for PE in medicine development with aligned value will serve as the foundation and first step towards the development of a master PE method and process framework covering all stages of the medicine development lifecycle (Boutin et al., 2017; Lamberti & Awatin, 2017; Lowe, 2016). The present study, therefore, aims to add to the body of knowledge in this field by addressing this critical knowledge gap through RO3 (see discussion in Section 6.3).

From a practical perspective, drawing on the insight that value perceptions of PE in medicine development differ depending on perspective and context (i.e. society, patients or PHARMA), it is essential to address the multidimensionality of value within PE in medicine development from a VCC perspective regarding: (i) what kind of value PE offers and for whom; (ii) which actors are involved in the value-creation processes (i.e. by what kind of resources), and (iii) how resources from different actors are integrated to realize their value potentials (i.e. through what kind of mechanism) (Kelly et al., 2015; Saarijarvi et al., 2013). These insights provided further motivation to develop theoretical propositions (see further discussion in Section 6.4) and practical recommendations to guide diverse stakeholders (i.e., POs, PHARMA, policy and healthcare authorities) regarding PE in medicine development from a value-creation perspective (see further discussion in Section 7.3).

The identified barriers and facilitators regarding PE in medicine development are carried over and further interrogated with the empirical data from the fieldwork (see Chapter 5) to create a final integrated analysis (see Chapter 6). The purpose is to inform the development of a final PE conceptual framework and theoretical propositions in medicine development (RO3 of the present study) based on aligned understandings – both from the literature and stakeholders' perspectives.

4.4 Surrogate terms and related concepts to PE in medicine development

To further clarify a concept, Rodgers (1989) suggested collecting data regarding the surrogate terms and related concepts. Surrogate terms are other means of expression addressing similar concepts and/or phenomena, which may share the same attributes and, as such, are interchangeable with the selected concept of interest. The notion of surrogate terms draws on the position that there may be several ways of expressing the same idea using different terminology (Rodgers, 1989; Walker & Avant, 2011). Several surrogate terms associated with the concept of PE in medicine development were found through thematic analysis of the literature data in the present study, and these are presented with descriptions and key references in ***Table 8*** and discussed further in the following paragraphs.

The surrogate terms found (see ***Table 8***) were considered as sharing the core attribute of co-creation through interaction with patients with the concept of PE in medicine development (Hibbard et al., 2004; Gruman et al., 2010; Bright et al., 2010; Boudes et al., 2018; Chiauzzi et al., 2016; Burns et al., 2014; Bloom et al., 2018; Kohler et al., 2017). As such, these surrogate terms were often used interchangeably with the concept of PE in medicine development in the current literature, however, without an in-depth understanding of the meaning and conceptual focus of these terms. The different nuances and varied conceptual focus of these surrogate terms are elucidated below.

A further examination of these surrogate terms revealed that each term has a different nuance in terms of its conceptual and contextual focus, when compared with the concept of PE in medicine development: (i) patient activation relates primarily to the cognitive and behavioural components of patients' attitudes towards healthcare (Carman et al., 2013; Danis & Solomon, 2013; Graffigna, Barello, Bonanomi & Lozza, 2015; Gruman et al., 2010; Hibbard et al., 2004); (ii) patient involvement exists on a PE continuum, from being passive recipients of information through to becoming an active partner through interaction with HCPs (Boudes et al., 2018; Bright et al., 2015; Carman & Workman, 2017; Gallivan et al., 2012); (iii) patient consultation describes the reactive role of patients in providing information or feedback, without involvement in decision-making (Armstrong et al., 2017; Carman & Workman, 2017; Deverka et al., 2012); (iv) patient empowerment focusses on the patients' subjective sense of control over their own disease and their feeling of being responsible for their own treatment outcome (Aujoulat, d'Hoore, & Deccache, 2007; Barello et al., 2015; Chiauzzi et al., 2016); (v) patient participation primarily refers to patients taking an active role in relational patient-doctor exchanges, which allow shared treatment decision-making (Barello et al., 2015; Bright et al., 2015; Burns et al., 2014; Wellard, Lillibridge, Beanland & Lewis, 2003); (vi) patient compliance and adherence refers to patients' behaviour in healthcare and medicine in terms of following the clinician's recommendations (Akhmetov & Bubnov, 2017; Barello et al., 2015; Bright et al., 2015; M. T. Brown & Bussell, 2011); and (vii) patient partnership recognizes that patients have assets, such as experiential knowledge and capacity, which can add value in medicine and healthcare through collaboration (Bright et al., 2015; Crawford et al., 2017; Perfetto & Oehrlein, 2015; Kohler et al., 2017; Loeffler et al., 2013) (see ***Table 8***).

Furthermore, these surrogate terms reflected the multi-faceted characteristics, context-dependence, and significance of the concept of PE, as demonstrated by its wide

usage across multiple disciplines and from different theoretical perspectives. For example, *patient involvement* was frequently used in the healthcare sector, drawing upon the notion of patients as being active partners in the *co-design* and *co-production* of healthcare services (Beier et al., 2019; Seerada et al. 2020), which finds its scholarly origin in the patient-centred care (Halabi et al., 2019; Sacristán et al., 2016; Wale et al., 2021), and public and patient involvement (PPI) in the public health sector (Abelson et al., 2016; Biddle et al., 2020; Smits et al., 2020). In recent years, *patient engagement* has increasingly been used as a contemporary term to describe the changing role of patients in the context of medicine development, who are expected to *share the joint leadership and decision making* together with HCPs across the medicine development lifecycle (i.e. research and development, regulatory review and approval, health technology assessment, market access and commercialisation) to *co-create* value for patients and all stakeholders (Borup et al., 2016; Grine et al., 2020; Lowe et al., 2016). The different terms used to describe patient participation in the specific context of use (i.e., patient involvement in the public health and healthcare services, and patient engagement in medicine development) are distinguished by their respective scholarly origin and practical relevance, with PE gaining increasing significance for both scholars and practitioners in the context of medicine development (Harrington et al., 2020; Majid, 2020; Vat et al., 2019).

Additionally, these surrogate terms for the PE phenomena suggested a gradual conceptual evolution in the behaviour characteristics of patients (such as compliance, adherence, activation, empowerment, participation) towards an emphasis on partnership with patients by all healthcare stakeholders (including PHARMA). This provides further evidence of the influence of the paradigm shift in healthcare towards VBM on the conceptualization of the PE phenomenon over the past decade (Bae, 2015; Marzorati & Pravettoni, 2017; Riva & Pravettoni, 2016).

Table 8: Surrogate terms for the concept of PE in the context of medicine development

Surrogate Term	Description	Key References
Patient Activation	…is related to the cognitive and behavioural components of patients' attitudes toward healthcare and is conceptualised as an incremental attitude that the patient may develop through interaction with HCPs.	Hibbard et al. (2004); Gruman et al. (2010); Danis & Solomon (2013); Carman et al. (2013); Graffigna et al. (2015)
Patient Involvement	…exists on a continuum with patient from being passive recipients of information through to becoming an active partner in interaction with HCPs.	Gallivan et al. (2012); Bright et al. (2015); Carman & Workman (2017); Boudes et al. (2018)
Patient Consultation	…patients are involved in a reactive role in providing information or feedback without being involved in decision-making through interaction with HCPs.	Deverka et al. (2012); Carman & Workman (2017); Armstrong, Rueda, et al. (2017)
Patient Empowerment	…describes the patients' subjective sense of control over their disease and treatment management and the feeling of being responsible for their health outcomes through interaction with HCPs.	Aujoulat et al. (2007); Barello et al. (2015); Chiauzzi et al. (2016)
Patient Participation	…implies the patient is in an active role, refers to a relational patient-doctor exchange that allows shared treatment decision-making through interaction with HCPs.	Wellard et al. (2003); Burns et al. (2014); Bright et al. (2015); Barello et al. (2015)
Patient Compliance/ Adherence	…focuses on the behavioural components of the patients' care experience referring the extent to which the patient's behaviour matches the clinician's recommendations through interaction with HCPs.	M. T. Brown & Bussell (2011) Barello et al. (2015); Bright et al. (2015); Akhmetov & Bubnov (2017)
Patient Partnership	…recognises that patients have assets, such as experiential knowledge and ability, which can be brought to add value in medicines and healthcare through interaction with HCPs.	Bright et al. (2015); Perfetto & Oehrlein (2015); Crawford et al. (2017); Kohler et al. (2017)

Furthermore, Rodgers (1989) suggested the identification of concepts related to the concept of interest as an important contribution to concept development (see discussion in Section 3.4 and ***Table 5***), helping to situate the concept of interest in the context of a broader knowledge base. Related concepts are those that 'bear some relationship to the concept of interest but do not seem to share the same set of attributes' (Rodgers & Knafl, 2000, p. 92). The identification of related concepts is based on the philosophical position that a network of related concepts adds contextual basis to the concept of interest and allows theory construction based on these conceptual relationships (Boyatzis, 1998; Rodgers, 1989; Walker & Avant, 2011).

Following an inductive thematic analysis of the literature, nine key concepts derived from the core themes regarding the antecedents, attributes and consequences of PE in

medicine development at the level of the patient, society and PHARMA (see discussion in Section 4.2 and ***Figure 8***) were identified as closely related to the concept of PE in the context of medicine development (see summary in ***Table 9***):

(i) ***Patient as consumer and expert***: this refers to the ethical argument that patients are consumers of healthcare, having the right for PE in medicine development that impacts on their life; patients have unique experiential knowledge and are experts whose input should be regarded as an asset and captured through PE in medicine development (Adams & Petersen, 2016; Armstrong et al., 2017; Champagne et al., 2015; Tapp et al., 2017). Acknowledging the patient as consumer and expert were suggested as a key antecedent of PE in medicine development at the patient level from the theoretical phase of the present study (see Section 4.2.2).

(ii) ***Value-based medicine***: this refers to the paradigm shift in healthcare which places patient value at the core and proposes that healthcare value should be measured by the health outcomes achieved around each patient (Bae, 2015; Batalden et al., 2016; Bloom et al., 2018; Riva & Pravettoni, 2016). The paradigm shift to VBM was suggested as a key antecedent of PE in medicine development at the society level from the theoretical phase of the present study (see Section 4.2.1).

(iii) ***Patient centricity***: this refers to a company's strategy and culture in which the needs of patients and carers are as important to a company's thinking and actions as the need for profit, permeating and informing all aspects of the business (Blasimme & Vayena, 2016; Hunter et al., 2015; Loeffler et al., 2013; Mitchell et al., 2017). The adoption of a patient-centric culture and strategy by PHARMA was suggested as a key antecedent of PE in medicine development at the PHARMA level from the theoretical phase of the present study (see Section 4.2.3).

(iv) ***Patient as value co-creator***: this refers to the appreciation that patients' experiential knowledge as an asset and resource, which should be brought into medicine development to maximize healthcare outcomes (Croft and McLoughlin, 2015; Kelly et al., 2015; Marzorati & Pravettoni, 2017; PFMD, 2018). The patient as a value co-creator was considered a key attribute of PE in medicine development at the patient level from the theoretical phase of the present study (see Section 4.2.2).

(v) ***Partnership and collaboration***: this refers to the interactions between patients and HCPs through shared leadership and joint decision-making, based on principles of reciprocity, respect, trust, co-learning, equality and transparency (Laurance et al., 2014; Perfetto and Oehrlein, 2015; Sacristán et al., 2016; Smith et al., 2015). Partnership and collaboration were indicated as key attributes of PE in the context of medicine development at the society level from the theoretical phase of the present study (see Section 4.2.1).

(vi) ***Integration of patient value***: this refers to a means of interactions with patients to incorporate patient input, experience and needs into the medicine development life cycle (Chiauzzi et al., 2016; Graffigna & Barello, 2015; Marzorati & Pravettoni, 2017; von Tigerstrom, 2016). The integration of patient value into the medicine-development process was suggested as a key attribute of PE in the context of medicine development at the PHARMA level from the theoretical phase of the present study (see Section 4.2.3).

(vii) ***Patient value****:* this refers to the unique preferences, expectations and experiences of individual patients towards medicinal products and treatment (M. M. Brown & Brown, 2013; Marzorati & Pravettoni, 2017; Sackett et al., 2000). Improved patient value was suggested as a key consequence for the concept of PE in the context of medicine development at the patient level from the theoretical phase of the present study (see Section 4.2.2).

(viii) ***Healthcare value****:* this refers to positive results collectively in patient outcomes, safety and satisfaction at a reasonably affordable cost, in association with a medicinal product and/or treatment (Anderson et al., 2014; Bae, 2015; Kelly et al., 2015; Porter, 2010). Improved healthcare value was suggested as a key consequence associated with the concept of PE in medicine development at the society level from the theoretical phase of the present study (see Section 4.2.1).

(ix) ***Business value***: this refers to the expected positive consequences associated with PE in medicine development for PHARMA in terms of better innovation, improved reputation and trust and financial benefits (Graffigna & Barello, 2015; Kendell et al., 2014; Kohler et al., 2017; Pitts, 2016). Improved business value was suggested as a key consequence of PE in medicine development at the PHARMA level from the theoretical phase of the present study (see Section 4.2.3).

These identified related concepts, associated with the concept of PE in medicine development (see ***Table 9***), are carried over and corroborated with the empirical data gathered from the fieldwork phase (see Chapter 5), and further elaborated and interpreted in relation to the theoretical perspectives (based on VBM, VCC and SDL) in the final analytical phase (see Chapter 6) with the aim of developing a final conceptual framework for PE in medicine development with theoretical propositions, thereby addressing RO3 of the present study.

Table 9: Key related concepts to the concept of PE in medicine development derived from theoretical phase

Related Concepts	Descriptions	Key References
Patient as consumer and expert	…refers to the ethical argument that patients are consumers of healthcare with the right to take part in PE in medicine development that affects on their life; and patients have unique experiential knowledge as experts whose input should be captured through PE in medicine development	Champagne et al. (2015) Adams & Petersen (2016) Tapp et al. (2017) Armstrong et al. (2017)
Value-based medicine	…refers to the healthcare paradigm shift with patient value at the core for all stakeholders and the proposition that healthcare value should be measured around the health outcomes achieved around patients.	Bae (2015) Riva & Pravettoni (2016) Batalden et al. (2016) Bloom et al. (2018)
Patient centricity	…refers to a company strategy which puts the needs of patients and carers at the centre of a company's thinking and actions, equal to the need for profit, permeating and informing all aspects of the business	Loeffler et al. (2013) Hunter et al. (2015) Blasimme & Vayena (2016) Mitchell et al. (2017)
Patient as value co-creator	…refers to the belief that patients' experiential knowledge is asset and resource; they should be brought into medicine development as co-creators to maximise healthcare outcomes.	Kelly et al. (2015) Croft and McLoughlin (2015) Marzorati and Pravettoni (2017) PFMD (2018)
Partnership & collaboration	…refers to the interaction between patients and HCPs through shared leadership and joint decision-making based on principles of reciprocity, respect, trust, co-learning, equality, and transparency	Laurance et al. (2014) Perfetto and Oehrlein (2015) Smith et al. (2015) Sacristán et al. (2016)
Integration of patient value	…refers to a means of interaction with patients to incorporate patient inputs, experience and needs into the medicine development life cycle.	Graffigna and Barello (2015) Chiauzzi et al. (2016) von Tigerstrom, (2016) Marzorati and Pravettoni (2017)
Patient Value	… refers to the unique preferences, expectations, and experiences of individual patients towards medicinal products and treatments.	Laurance et al. (2014) Dewulf (2015) Batalden et al. (2016) Pitts (2016)
Healthcare Value	… means the positive results in collective patient outcomes, safety, and satisfaction at an affordable cost, in association with a medicinal product and/or treatment.	Kendell et al. (2014) Graffigna & Barello (2015) Pitts (2016) Kohler et al. (2017)
Business Value	…refers to the expected positive consequences associated with PE in medicine development for a PHARMA company in terms of better innovation, improved reputation, and financial benefits.	Dewulf (2015) Miseta (2015a) Kirwan et al. (2017) Levitan et al. (2018)

4.5 Empirical examples of the concept of PE in medicine development

Rodgers and Knafl (2000, p. 96) recommend the identification of empirical exemplars as a useful part of concept development 'to provide a practical demonstration of the concept in a relevant context; …to illustrate the characteristics of the concept in relevant contexts and, as a result, enhance the clarity and effective application of the concept of interest.' (see discussion in Section 3.4 and ***Table 5***). Following Rodgers' (1989) approach, several empirical exemplars related to the concept of PE in medicine development were

identified from the current literature, addressing key aspects (i.e., attributes, antecedents, and consequences) of the concept of PE in medicine development. These exemplars offered empirical evidence and practical illustrations of the concept of PE in medicine development, strengthening understandings and delineating further their links to the theoretical perspectives based on VBM, VCC and SDL (see Section 2.5).

At the PHARMA level, taking a value co-creation (VCC) theoretical perspective, a real-life exemplar (based on workshops and online survey with n=1195 patients and carers) offered by Yeoman et al. (2016) illustrated the key attribute of the concept of PE in terms of partnership and collaboration throughout the medicine development process. The study showed the effective application of PE in areas such as prioritisation in the medicine development pipeline, understanding the patient journey, advocating health policies in patients' interests, and co-creating solutions with patients (Yeoman et al., 2016). Another practical exemplar from a PHARMA company Sanofi by Miseta (2015a) linked the co-creation activities within PE in medicine development with the key operational principles of a PHARMA company in terms of understanding patients' need, developing solutions and driving outcomes and developing a patient-centred organisation. The above two practical exemplars illustrate the core attribute of PE in medicine development (i.e., *co-creation*) and the essential link between PE in medicine development and the underlying VCC theoretical core (i.e., *co-creation*), adopted as a theoretical perspective for the present study.

At the patient level, drawing on a VBM theoretical perspective, an exemplar from Kelly et al. (2015) demonstrated how different value definitions from stakeholders underpin different priorities and ethical judgements, underscoring the need for all stakeholders to take an aligned patient-centric stance as a core antecedent to the concept of PE in medicine development. Furthermore, an exemplar from Marzorati and Pravettoni (2017) illustrated how VBM drove healthcare and medicine towards a patient-centred paradigm, and further

demonstrated that *patient centricity* is a necessary core antecedent of the concept of PE in medicine development. Additionally, this exemplar indicated achieving positive patient value and healthcare value as logical consequences of PE in medicine development (Marzorati & Pravettoni, 2017), which further substantiated the association between the concept of PE and VBM theory - both share the theoretical core of a focus on patient value and healthcare value in the context of medicine development.

At the society level, a PE model in medicine development was presented by Perfetto and Oehrlein (2015), aiming for effective implementation of patient-focused drug development (PFDD) as required by recent FDA guidelines (FDA, 2016, 2018a, 2018b). This proposed PE model (Perfetto & Oehrlein, 2015) covered the preparation, execution and communication phases in the medicine development life cycle and depicted the potential patient input that PHARMA could incorporate into its medicine development activities. Key elements of PE in medicine development derived from this model were (i) patient focus (or *patient centricity* – defined as a key antecedent of the concept of PE in the present study); (ii) patients as partners (which concurred with the defining attribute of the concept of PE in the present study – *partnership and collaboration*); (iii) meaningfulness of PE in terms of the development of science-based methods for gathering patient perspectives (which concurred with the theoretical implication derived from the present study – to develop a methodology for PE); and (iv) regulatory and market-based incentives needed to generate benefits for all participants (Perfetto & Oehrlein, 2015), which concurred with the identified consequences of PE in medicine development in the present study – to *improve patient value, healthcare value and business value.* This empirical study by Perfetto and Oehrlein (2015) was conducted within the disciplinary domain of regulatory science and resonated with the PFDD initiatives from the FDA (FDA, 2016, 2018a, 2018b), which exemplified the current understanding of PE in medicine development from a regulatory aspect at the societal level.

Another real-life exemplar from Messina and Grainger (2012) (based on interviews with *n*=39 healthcare stakeholders) demonstrated the following key elements of the concept of PE in medicine development from the HTA perspective: (i) patient experience should be incorporated into the HTA processes of medicine to reflect patient centricity (which resonated with *patient centricity* as an antecedent to the concept of PE as identified in the present study); (ii) PHARMA should integrate the patient voices into medicine development processes through co-creation of patient value (which concurred with the *co-creation* as a key attribute of the concept of PE as identified in the present study), and (iii) processes should be improved to increase transparency and facilitate impact measurement associated with PE in value delivery (which concurred with the claimed *improved value* as a consequence of the concept of PE identified in the present study).

4.6 Summary

In the theoretical phase in the present study, an inductive thematic analysis of the literature data following the evolutionary concept development approach of Rodgers (1989) offered insights into the antecedents, attributes, consequences, surrogated terms, related concepts, empirical exemplars and influencing factors associated with PE in medicine development (RO1 of the present study). As a result, *co-creation* was identified as an overarching key attribute of the concept of PE in medicine development, while *patient-centricity* was identified as an overarching key antecedent and *improved value* as an overarching key consequence of the concept of PE in this context. Based on the above understandings, a provisional thematic map of PE in medicine development from a value-creation perspective was developed (see ***Figure 8***), which has addressed RO1 of the present study.

The theoretical phase of the present study provided a comprehensive understanding of the antecedents, attributes, consequences and influencing factors associated with the

concept of PE in the context of medicine development. This understanding offered a piece of original work in providing a collective, contemporary meaning for the concept of PE in medicine development, which had been considered as missing in the present literature and is an important starting point for the development of a concept (Beecher et al., 2017; Penrod and Hupcey, 2004; Rodgers & Knafl, 2000; Schwartz-Barcott & Kim, 1986; Walker and Avant, 2011).

5 Analysis and findings from the fieldwork phase

5.1 Introduction

This chapter presents the analysis and findings derived from the thematic analysis of the interviews, which aimed to capture experiences and perceptions of PE in medicine development from relevant stakeholders (i.e., patients, medicine developers, and PE experts). Exploring the understanding of PE in medicine development from the perspectives of key stakeholders resonates with my social constructivist stance: PE in medicine development is a complex social phenomenon and the conscious interpretation of experiences from key actors will enrich the understanding of this concept in practice. In addition, concept development based on real-life experience is considered much more valuable than the usual approach via the literature analysis, because it may produce insights into how the concept is constructed by individuals which 'can be a powerful heuristic to promote understanding and the further growth of knowledge' (Rodgers & Knafl, 2000, p. 100). Exploring understandings of key stakeholders is expected to offer rich and deep insights into how the concept of PE is constructed by practitioners within the context of medicine development, and how these constructed meanings could support the conceptualization of PE in medicine development, which is considered vague and fragmented in the current literature (Higgins et al., 2017; Hoos et al., 2015; Perfetto et al., 2015). Accordingly, the insights regarding PE in medicine development generated through interviews with stakeholders are analysed and presented in this chapter to address RO2 of the present study: to explore practices and perceptions regarding PE in medicine development from the perspectives of key stakeholders.

To this end, interviews with key stakeholders were conducted. The thematic analysis of these interviews led to the development of a second thematic map from the fieldwork. The identified core themes were interpreted from a value-creation perspective, supported by

analytical narratives and quotes from interview participants, and organized around the antecedents, attributes, consequences, barriers to and facilitators of the concept of PE in medicine development (see discussion in Section 5.2).

Building on the previous work from Barello et al., (2012) and Carman et al. (2013) on the PE continuum model (see discussion in Section 2.3 and ***Figure 2***), the thematic analysis of the interviews was organized and presented on three different levels – patients, society and PHARMA. Thus, the developed themes represent vivid perceptions of the empirical reality regarding PE in medicine development from multiple stakeholder perspectives at different levels, in order to explore both the variant and common understandings of the concept of PE in medicine development by different stakeholders.

Individual semi-structured interviews with 32 participants (for interviewee profiles see Section 3.5.3 and ***Table 6***) allowed both sufficient variability and data saturation for inductive theory-building (Bryman, 2016). All interviews went smoothly, and interviewees showed great motivation and willingness to share their experiences of PE in medicine development, appreciating the opportunity to participate in the present research. This offered further evidence of the relevance and significance of PE in medicine development to the stakeholders, which is believed to have the potential to change medicine development practices in the coming years and offer significant benefits to all stakeholders. The relevance of PE in medicine development was described by one participant as follows:

> *PE is the right thing to do for the patient at the bottom line. I think the benefits could be innovation, if we use a human-centric design approach based on PE throughout the drug development processes, which will pay off enormously.* [P-04 (PX)]

This respondent mentioned two important aspects associated with PE in medicine development: (i) '*what*': PE is the right thing to do for the patient; (ii) '*how*': PE follows a

human-centric design approach throughout the medicine development processes to enhance innovation and generates positive benefits. It became clear that the questions about *what* and *how* concerning PE in medicine development guided participants in constructing the meanings of this PE phenomenon in medicine development. These underlying questions coincide with the ROs in the present study, which aim to explore an understanding of the PE phenomenon in medicine development from the perspectives of the relevant stakeholders. In the next section, the findings from the thematic analysis of interviews are presented, interpreted, and discussed from a value-creation perspective.

5.2 Thematic map of PE in medicine development developed from the fieldwork

Drawing on the research methodology framework based on Rodgers' (1989) concept development approach (see ***Table 5***), inductive thematic analysis of the interview data from the fieldwork was conducted. Throughout this process, interview transcripts were read line by line, repeatedly, analytical notes were generated to mark the significance of certain text passages and to document the researcher's thoughts and observations with reference to the research questions. Codes were developed throughout these reading and coding processes. Recurring motifs across the codes were then identified to develop categories that offered a broader and more abstract theoretical understanding of the interview data, and this was constantly compared and interpreted in relation to the research questions of the present study. In so doing, themes were further developed through the analysis and interpretation of the defined categories and codes, which were derived from an iterative process of reading and rereading, coding and recoding, until the emergence of a coherent coding book, documenting the relationships among the themes, categories and codes with descriptions (see ***Annex 9***).

Bazeley (2013) argued that researchers should not simply specify themes that have been identified but justify why these themes are significant by showing how they relate to other themes and research objectives. Following this suggestion, the processes of coding and

generating categories and themes in relation to the RO2 were undertaken iteratively with the support of the NVivo system, which provides a transparent audit trail to support the justification of how themes were identified in the fieldwork. Identified themes from interviews were then organized into the key aspects of PE in medicine development (i.e., the antecedents, attributes, consequences, barriers and facilitators) according to the research methodology framework (see ***Table 5***) to address the RO2 of the present study.

As a result of this thematic analysis of interviews, a second thematic map concerning the concept of PE in medicine development was developed (see ***Figure 9***). The key aspects regarding the concept of PE in medicine development were identified as follows:

(i) the core antecedent of the concept of PE in medicine development was 'the presence of patients' voices in medicine development in the shift to a VBM paradigm' (supported by 32 sources with 345 references through the thematic analysis of interview data), which is discussed further in Section 5.2.1;

(ii) the core attribute of the concept of PE in medicine development was evidenced as 'co-creation through combining the knowledge and experiences of PHARMA and patients in interactions' (supported by 32 sources with 377 references through the thematic analysis of interview data), which is discussed in detail in Section 5.2.2;

(iii) the core consequence of the concept of PE in medicine development was identified as 'improved value for patients and all healthcare stakeholders' (supported by 23 sources with 124 references through the thematic analysis of interview data), which is further discussed in Section 5.2.3;

(iv) the major barrier to the concept of PE in medicine development was identified as 'value discrepancy, challenges in methodology, process and culture'

(supported by 30 sources with 235 references through the thematic analysis of interview data), which is further expanded in Section 5.2.4;

(v) the major facilitator for the concept of PE in medicine development was suggested to be 'develop aligned PE framework with multiple stakeholders throughout the medicine development lifecycle' (supported by 28 sources with 140 references through the thematic analysis of interview data), which is discussed further in Section 5.2.5.

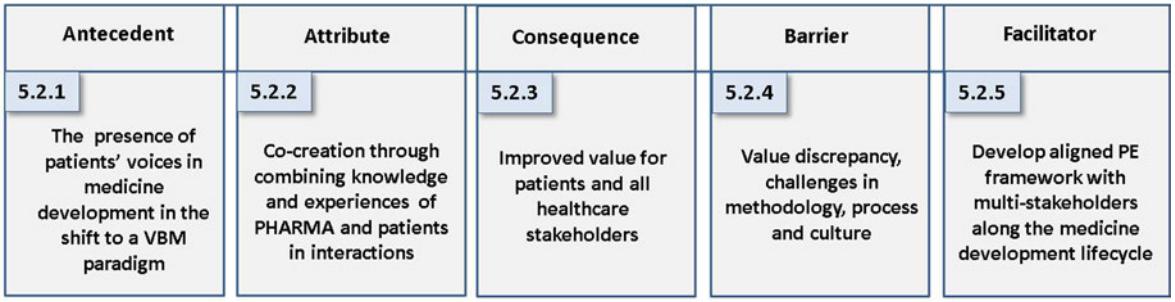

Figure 9*: Thematic map of PE in medicine development developed from the fieldwork*

The core themes identified above concerning the concept of PE in medicine development were built on the categories and codes generated from the inductive thematic analysis of interview data, which are presented and discussed further in the next sections to address RO2 of the present study (see Section 1.2).

5.2.1 *Antecedent:* the presence of patients' voices in medicine development in the shift to a VBM paradigm

Antecedents are events that must occur before the occurrence of the concept and describe the important prerequisites for a concept to take place (Rodgers & Knafl, 2000). Substantial evidence was offered by the interviewees to support the claim that the paradigm shift to VBM in healthcare requires the presence of patients' voices in medicine development, and this was suggested as a core antecedent to the concept of PE in the context of medicine development:

We are all moving towards the value-based reimbursement system; … If you are going to design the positive outcome for patients as value, you need to do it with patients' voices as part of the medicine development processes. [P-06 (PX)]

Healthcare is going in the direction of incorporating patients' voices in the evaluation of benefits-risks of therapies, and it is great it goes in that way which is helpful to patients; … this is coming from the recognition that healthcare quality and treatment outcomes can be improved if you get patients engaged. [P-04 (PX)]

The above two patient expert interviewees referred to the emphasis on incorporating patients' voices in medicine development in the shift to a VBM paradigm that will require PE in medicine development. Furthermore, the two interviewees suggested that the VBM paradigm requires patients' voices being integrated into the reimbursement assessment (of HTA) and the benefits-risks evaluation of therapies by regulators (of HA), which are the two most important regulatory instruments guiding PHARMA's medicine development practices. Thus, the paradigm shift to VBM was perceived as an impactful antecedent to the concept of PE in medicine development, requiring the presence of patients' voices in medicine development within PE.

Furthermore, this identified core theme concerning the antecedent of PE in medicine development – *the presence of patients' voices in medicine development in the shift to VBM paradigm* – was supported by categories, identified as antecedents of PE in medicine development at the level of the patient, society, and PHARMA respectively, as follows (see ***Figure 9.1*** and ***Annex 9)***:

(i) 'patient as consumer and expert wants patients' voices to be heard', at the patient level (supported by 29 sources with 127 references through the thematic analysis of interview data);

(ii) 'regulators and HTA ask for the presence of patients' voices in medicine development', at the societal level (supported by 30 sources with 99 references through the thematic analysis of interview data); and

(iii) 'PHARMA to adopt patient-centricity to understand patients' needs and perspectives', at the PHARMA level (supported by 30 sources with 116 references through the thematic analysis of interview data).

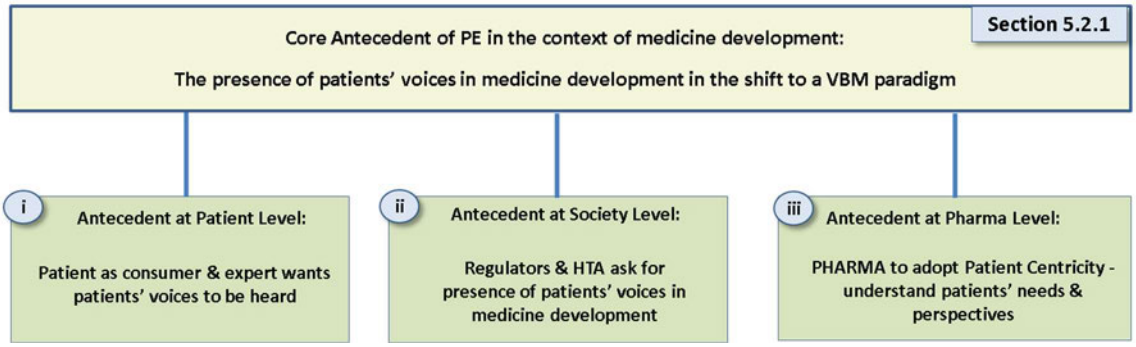

Figure 9.1*: Antecedents of PE in medicine development identified from the fieldwork.*

These categories and core themes, identified from the interviews concerning antecedents of PE in medicine development, concurred significantly with previous discussions from the theoretical phase in the present study (see Section 4.2), which will be further discussed in the final analytical phase (see Chapter 6). As such, interviewees offered further rich and vivid accounts of the PE phenomenon that promoted understandings through practical experience. The antecedents of PE in medicine development identified from the fieldwork at the level of the patient, society and PHARMA are expanded further in the following paragraphs, supported by narratives from the interviewees and interpreted in relation to the research questions of the present study from a value-creation perspective.

(i) '<u>Patient as consumer and expert wants patients' voices to be heard</u>' – an antecedent of PE in medicine development at the patient level

Interviewees perceived that the role of patients in the context of medicine development has been changing with the shift to a VBM paradigm, which has framed patients as consumers and experts with rights and responsibilities for their own health and healthcare. The patient as consumer and expert, in this context, was evidenced as an antecedent to the concept of PE in medicine development at the patient level, as elaborated by some interviewees:

> *Taking a human-centred design thinking approach, requiring that you really adopt an attitude of empathy, to acknowledge that patients are the expert in their disease.* [P-02 (PX)]

> *Value for patients means that patients' opinion should be more taken into account by PHARMA and patients should be treated as customers and stakeholders.* [P-08 (MD)]

> *Following the civil rights movement and patients' movement about 'nothing about me without me', PHARMA should consider the movement of patients seriously, since they are the ultimate healthcare beneficiary and consumers. The other commercial industry has made good examples in engaging consumers to design consumer experiences;* PHARMA *needs to deliver these patient experiences as well, starting with engage patients to understand what their needs are and what therapy are important for patients to be developed.* [P-02 (PX)]

We are moving to an era of personalised medicine; you cannot develop personalised medicine unless you can identify the specific needs of the individual patients. Patients are consumers, so what the consumers really expect and accept from the new medicinal treatment should play an important role for PHARMA to develop personalised medicine for patients. [P-32 (PX)]

Here, these interviewees addressed the patients' roles as consumers and experts to justify the need for PE in medicine development at the patient level, to develop better medicines that can fulfil patients' needs. They also argued that other industries are much more advanced in designing consumer experiences. Recognizing patients as consumers and experts is therefore the starting point for PHARMA to adopt PE in medicine development and learn from the other industries in terms of customer engagement experiences.

Moreover, the interviewees emphasized that empowered patients with increased health literacy and ability want their voices to be heard; they want to be involved in medicine development processes, since these will affect on their lives:

I think PE is derived from the patient and public involvement (PPI) considering the patients' right to be involved, which is a helpful ethical and humanitarian consideration; if the PHARMA company really want to engage patients, they will treat patients as partners through cooperation to make sure the relevance of their research. [P-11 (PX)]

Start with empowering people with different access allowed patients' voices to be expressed and mirrored with medication and services they want, ... so that a democratisation of information and access, and a communication mechanism that

has brought patients' perspectives more to the surface and visible than ever before, and this has changed the power dynamics. [P-12 (PT)]

I see the emerging patient research partner network built up by the patient organisations across almost all disease areas, which continually built up both scientific rigor and transparency in their activities; and patients are ready to collaborate as research partners and co-produce evidence in medicine development. [P-16 (PX)]

The above interviewees addressed the increased power and visibility of patients and POs within the new VBM era, rooted in the recognition of the patient as a consumer and expert who has the right and assets to take part in PE in medicine development. This has been a new movement in the past decade at the patient level and was shown as a key antecedent of PE in medicine development at the patient level.

Furthermore, patients' experiential knowledge in living with a disease was recognized by most interviewees to be an asset which should be captured to inform the development of better medicine, thus substantiating the claim that 'the presence of patients' voices in medicine development in the shift to a VBM paradigm' as a core antecedent for the concept of PE in medicine development at the patient level. Some interviewees offered their perspectives to further expand this theme:

From a moral perspective, it is patient who bears the impact of the treatment, it's a moral imperative to inform, engage, and involve patients along the medicine development lifecycle incorporating patients' inputs regarding the benefits-risks-assessment (BRA) of a medicine. [P-04 (PX)]

> *We as patient organisations need to think about how to better utilise the patient data as asset and use these data for good and generate benefits for patients ultimately; … some good examples of patient organisations are that they started to quantify the patients' perspectives, so that patients' perspectives can contribute in a sustainable way that fits into the medicine development in the PHARMA company and the review processes with science-based methodology.* [P-12 (PT)]

Drawing on the above narratives from interviewees, the notion of the patient as consumer and expert was emphasized to delineate the new role that patients have been adopting within the new VBM paradigm. Justifications for this new patient role were offered from different perspectives by interviewees, including moral considerations from a social justice perspective, expectations from a consumer perspective and value-creation from a value perspective. All these arguments offered by interviewees emphasized that recognizing the patient as a consumer and expert is an important antecedent of PE in medicine development at the patient level.

(ii) 'Regulators and HTA ask for the presence of patients' voices in medicine development' - an antecedent of PE in medicine development at the society level

At the societal level, interviewees clearly stated that regulators and HTA agents have been asking for presence of patient voices in the context of medicine development, and this was considered a major driving force and a core antecedent for the concept of PE in medicine development practices at the society level. Interviewees offered the following arguments:

I think there have been a number of legislative and cultural changes that account for the emphasis of PE in medicine development – beginning with FDA's draft guidance on patient-reported outcome in medicine development in late 1990s that strengthen the market pull towards inclusion of patients' perspectives, to the increased participatory research methods emphasised by HTA agencies – such as NICE, PCORI, and CIHR. [P-18 (PX)]

I think many PHARMA are interested in PE because FDA asked them to report evidence of PE in the medicine development, so it's beneficial for them to have these endpoints in mind; … definitely these requirements from regulators will accelerate the PE processes at PHARMA. [P-05 (PX)]

It will be helpful for regulatory agency to come up with some firm requirements regarding PE and ask PHARMA to demonstrate how they have incorporated patients' inputs in the product development lifecycle. [P-10 (PT)]

I think governmental regulatory agency clearly agree that the submission package needs to be enlarged to include this kind of patient-generated data, … PE is becoming an absolute must-do. Imagine that FDA has been mandated by legislation which provides an important and powerful place where patients voices are to be involved in the drug review processes; … the newest way of PE is to involve patients' voices in the regulatory and HTA decision making. … If PHARMA see that regulators are taking these PE *activities seriously, they are going to be more motivated to do the same.* [P-06 (PX)]

The above quotes from interviewees strongly support the claim that 'regulators and HTA ask for the presence of patients' voices in medicine development' at the society level, which can create a strong mandatory effect and trigger the introduction of PE in medicine development because, in the context of medicine development, regulators set the norms and policy which PHARMA's medicine development activities need to follow. Therefore, regulatory requirements for the presence of patient voices in medicine development was suggested as an antecedent to the concept of PE in medicine development at the society level.

(iii) '<u>PHARMA to adopt patient centricity - understand patients' needs and perspectives</u>' – an antecedent of PE in medicine development at the PHARMA level

At the PHARMA level, interviewees perceived that intrinsic motivations to understand patients' needs by PHARMA in taking a patient-centric attitude should be present to start authentic PE in medicine development. This was considered by most interviewees to be an intrinsic antecedent of PE in medicine development at the PHARMA level, which sets out the prerequisites for true adoption of PE by PHARMA in medicine development. Some narratives from interviewees are offered below to substantiate this claim:

> *PHARMA industry is changing from the blockbuster model which we saw in the 1980s and 1990s to a more patient-centric medicine development, which they did not give attention to in the past. The old fashion of paternalism in medicine development will not work anymore; instead, PHARMA needs to figure out what patients' needs are and match them with the new medical treatment to be developed.* [P-12 (PT)]

> *PHARMA would need to engage patients to design consumer experiences as in all the other commercial industry, as well as start to understand patients' needs and what are important for them in development of treatment therapy.* [P-02 (PX)]

I hope that PHARMA will do PE not just due to the societal pressure so that they have to do, rather do the PE out of the position to see that PE is actually useful to help them develop better medicine and get product approval which PHARMA has intrinsic motivation to do so. [P-27 (MD)]

The above interviewees explained that adopting patient-centricity in medicine development was perceived as necessary at the PHARMA level because the industry has moved away from a paternalist model towards a patient-centric one, which requires PHARMA to engage with patients and match patients' needs with the medicines developed. This narrative, therefore, supports the argument that patient-centricity at the PHARMA level is an important antecedent to PE in medicine development at the PHARMA level. Furthermore, these interviewees discussed the need for patient-centricity by PHARMA from the perspective that patients are consumers, so that PHARMA should have an intrinsic motivation to understand patients' needs through PE to develop useful medicines for their customers – the patients. And PHARMA can learn how to best design consumer experiences from the other industries which are much more advanced in this field:

Acknowledging that patients are the expert in their particular disease, patients can help PHARMA to understand what outcomes are important to them, what critical endpoints the research should work on, what are the scientific questions to be asked and how are they relevant to the different symptoms, so PHARMA needs PE to get these patients' inputs. [P-02 (PX)]

This interviewee emphasized the notion that patients are experts who can provide useful input to inform medicine development activities at the PHARMA level. Taking the above arguments from interviewees into account, PHARMA's intrinsic motivation to understand patients' needs to develop better, patient-centric medicine was suggested as a key antecedent to the concept of PE in medicine development at the PHARMA level.

Furthermore, the following relationships between these antecedents to the concept of PE in medicine development at different levels were suggested by interviewees: 'patients want their voices heard' was the first driving force for PE in medicine development at the patient level, followed by 'regulatory initiatives asking for PE in medicine development'. Lastly, driven by the appeal for PE by patients and regulators, PHARMA started to adopt a patient-centric attitude within PE in their medicine development processes. The relationship between these antecedents to PE in medicine development at different levels was vividly depicted by the interviewees based on their own experiences:

> *PE started as anecdote in the social media-driven by patients and was now moving towards including science-based patient voices into the medicine development, review, and approval processes. ... Regulators have understood that it is important that patients should have a voice in this. What happened in the last five years is that more and more patient groups are becoming more sophisticated and they understand their ability in influencing the drug review not just using emotion, but also through helping to collect data and sharing therapeutic experiences. ... and then I think PHARMA industry and the governmental regulatory agency agreed that the submission package needs to be enlarged to include this kind of patient-generated data. ... so, more and more people from PHARMA realised that the traditional way*

of drug development is no longer an optional proposition anymore, and PE was becoming an absolute must-do. [P-06 (PX)]

PE movement starts with the increasing importance of individual patient's expectation as a societal driver, which translates into the emergence of patient organisations as collective organised patients who can influence the healthcare policy and PHARMA's medicine development decisions. [P-30 (MD)]

My son was diagnosed having Duchenne muscular dystrophy disease twenty-five years ago, we did not know much about this disease and its therapy at that time, so I started raising fund and organising fundamental research on this disease, and also hiring lobbyist to influence US government to issue the Muscular Dystrophy Act which eventually came to the effect in 2000. As this disease section started growing and came to the tipping point that PHARMA industry became interested in research on this disease, we supported FDA in the development of treatment guidelines based on our understandings about this disease gathered over years and afterwards supported PHARMA to conduct patient preference studies. ... Now the US government started the patient-focused drug development (PFDD) program and it made me laugh a little bit if you think this is new [laughing], since we have been doing the PFDD in the Duchenne muscular dystrophy rare disease areas for more than twenty-five years. Nevertheless, since the release of the PFDD initiative by the US government, it seems that PE started to catch fire and became really a big deal now, and I am very happy about it. [P-17 (PT)]

The above illustrations from interviewees suggested that increased patient power and responsibility in healthcare was the primary driver of the PE phenomenon in medicine development, which has further influenced the policy shift in the regulators and the culture changes at PHARMA, attempting to adapt to the new patient-centric VBM medicine development paradigm. These insights from interviewees offered further evidence to support the claim that '*the presence of patients' voices in medicine development in the shift to a VBM paradigm*', was suggested as an overarching core antecedent to the concept of PE in medicine development from the fieldwork (see ***Figure 9.1***).

5.2.2 *Attribute*: Co-creation through combining knowledge and experiences of PHARMA and patients in interactions

Attributes are those defining characteristics of a concept that are always present in the concept (Walker & Avant, 2014). The thematic analysis of interviews in the present study confirmed that co-creation is an overarching core attribute of the concept of PE in medicine development, allowing the knowledge and experiences of PHARMA and patients respectively to be combined through interactions. The following three categories at the level of the patient, society and PHARMA, led to the development of the core attribute of PE in medicine development – '*co-creation through combining knowledge and experiences of PHARMA and patients in interactions*' (see ***Figure 9.2*** and ***Annex 9):***

(i) Patient as value co-creator **-** leverages patients' experience of living with disease as an asset at the patient level (supported by 27 sources with 66 references in the thematic analysis of interview data);

(ii) Patients as partner in medicine review and approval processes of regulators at the society level (supported by 17 sources with 33 references in the thematic analysis of interview data);

(iii) Presence of patients' voices in medicine development at the PHARMA level (supported by 31 sources with 274 references in the thematic analysis of interview data).

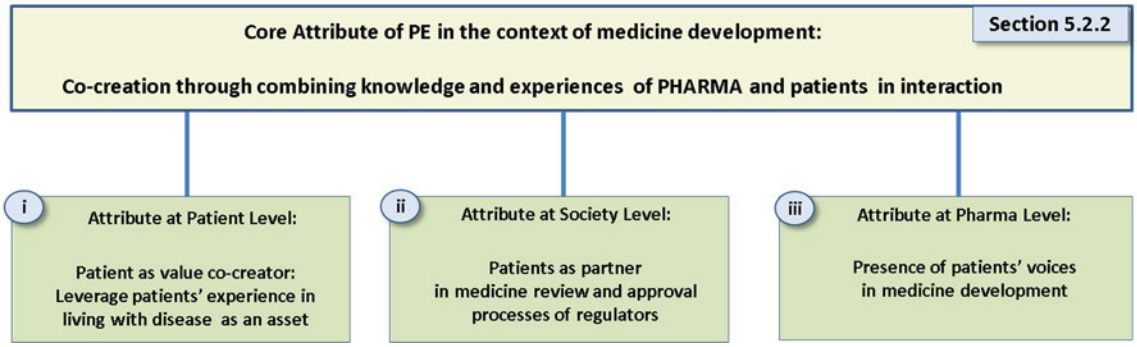

***Figure 9.2**: Attributes of PE in medicine development identified from the fieldwork.*

These identified categories and core themes concerning the attributes of PE in medicine development provided empirical evidence which supports similar themes derived from the thematic analysis of the literature (see Section 4.2). They further added practical insight and rich accounts to these themes, thus offering novel knowledge to expand understandings of the new PE phenomenon grounded in real-life experiences. The insights gathered from interviewees regarding the attributes of PE in medicine development are discussed and justified further in the following paragraphs.

(i) '<u>Patient as value co-creator: leverage patients' experience in living with disease as an asset</u>' – an attribute of PE in medicine development at the patient level

Interviewees explained in great detail why they perceived patients' experience of living with a specific disease as important information that should be captured and integrated into medicine development as valuable resources. As such, interviewees perceived that the patient as value co-creator in medicine development must be present within PE, to leverage patients' experience and deliver patient value, therefore it can be considered a key attribute of PE in medicine development at the patient level (supported by 27 sources with 64

references based on the thematic analysis of interview data) (see ***Figure 9.2*** and ***Annex 9***). Several arguments were offered by interviewees which demonstrate this core PE attribute in medicine development at the patient level:

> *For me, value ultimately means the positive outcome for patients. If you are going to design the positive outcome for patients as value, you would need to do it with patients' voices as part of the processes.* [P-06 (PX)]

> *In the past five years or so, there was increased appreciation to see patients as research partners and co-producers of evidence.* [P-18 (PX)]

> *PE started with the increasing importance of individual patient's experience as a societal driver. ... So, the idea of partnership between patients and PHARMA emerged, so that patients are not just research subjects, but they can be research partners to co-design the medicine.* [P-30 (MD)]

> *PE in the research refers to the active, meaningful, authentic, and collaborative interactions between patients and researchers across all the research stages, which is guided by patients' contributions, through recognising the unique patients' experiences, value and expertise.* [P-26 (PT)]

> *PE is about giving patients a seat at the table, so that we can capture patients' voices, insights, and experiences, and integrate all these patients' inputs into the study design, the product development, so that clinical trials are conducted with patients to optimise their clinical trial experiences and healthcare experiences.* [P-25 (PT)]

Acknowledgement of patients' expertise is important; ... you need to set up a structure to engage patients early on throughout the drug development at different interaction. [P-04 (PX)]

Having a patient advisory board is certainly a way that PHARMA can use PE, with this you can bring in more observations to understand how the living experiences of patients mean to the medicine development, patients are value co-creators in these actions, not just a research subject anymore. [P-05 (PX)]

As elucidated by the above interviewees, the patient as value co-creator was demonstrated to be a key attribute of PE in medicine development at the patient level, which was supported by the majority of interviewees drawing on the notion that patients' experiential knowledge of living with disease is a valuable asset. However, it is worth noting that most of these practical illustrations of the patient as value co-creator were provided by interviewees from the patient and PE expert groups, whereas some interviewees from the medicine developer group still expressed some scepticism about the value contribution of patients within PE in medicine development, as illustrated below:

To be honest, I think it will be difficult to let patients contribute to the research and clinical development of medicine without the necessary medical knowledge for them to identify what they really need. ... At the early research phase, even with the recognition that patients are customers and becoming knowledgeable, but still patients cannot provide the medical information as we get them from doctors. I am

not sure how useful can the inputs collected from patients be used in the medicine development. [P-21 (MD)]

Patients may ask for more money for participation in the clinical study through additional PE activities; but most of the idea patients give us, we can't act on from PHARMA's perspectives. Surely patients may get better treatment through their voices, but we as PHARMA have to pay for the additional PE activities, so I don't know if we should open it up. [P-22 (MD)]

At the early stage of drug development, it is about testing the efficacy and safety, … it might be not worthwhile to ask patients' perspectives at this early stage, because it is pretty science-driven activities and patients can provide limited inputs. … It is difficult to ask patients about their drug tolerability, they also do not know how to express it, because the feeling of patients is very subjective and different from individual to individual; … so to the scientific database, I think patients can not contribute. [P-15 (MD)]

As illustrated above, in contrast to the acknowledgement of *patient as value co-creator* by most interviewees, some interviewees in medicine development roles expressed doubts about the *patient as a value co-creator* in medicine development, using two principal arguments: (i) patients may not have the medical knowledge to bring their disease experience into a scientific domain, such as medicine development, and (ii) wishful thinking may lead patients to talk about what they want instead of what they need. While the scepticism of these medicine developer interviewees cannot be ignored, their narratives showed the underlying value perspective that drives their thinking towards scientific value in medicine

development rather than patient value. As seen in the theoretical phase, value discrepancy among healthcare stakeholders was suggested to be a key barrier to PE in medicine development; exploring PE in medicine development from the perspectives, including value perspectives, of different stakeholders is highly relevant in gaining a comprehensive understanding of the PE phenomenon. Consequently, compensating for the dominance of scientific value by integrating patient value into medicine development through PE is becoming even more important within a VBM paradigm with the emphasis on patient value. Therefore, the recognition of the *patient as a value co-creator* in medicine development by interviewees in this study was considered present within PE in medicine development at the patient level and identified as a key attribute.

Regarding to how value is defined in the context of medicine development, several interviewees illustrated the multiple value perception of diverse stakeholders, but emphasized that patient value is the primary goal that should unify the different value perspectives and determine the rewards for medicine development endeavour and consequently generate value for all healthcare stakeholders:

> *Understanding about what the unmet medical needs of patients are, what are the most value from the public health perspective, to understand what the gaps for patients first, keeping patients' hope involved in considering what need to be developed and then decide on the research priorities and pipeline. In my mind, this is the single most impactful actions which PE will bring value to patients and the public health*. [P-04 (PX)]

PE is about how you improve the patients' outcome – that is the only goal here. I don't think that there is disagreement that more robust scientific patients' voices data will drive positive outcomes, that's why PE needs to be encouraged. [P-06 (PX)]

With regards to treatment effect, it would be interesting to introduce health and well-being quality of life parameters in the medicine testing beyond efficacy and safety, because these are very patient-relevant reflecting patient value. [P-01 (MD)]

Concerning the question about how value can be co-created with patients within PE in medicine development, interviewees offered practical examples illustrating the multifaceted activities that patients can contribute value along the medicine development lifecycle in terms of co-prioritization, co-planning, co-implementation, co-dissemination, and co-measurement. Patient organisations were often suggested by interviewees as the intermediaries to establish multilateral partnership and collaboration with all healthcare stakeholders (including PHARMA) and to facilitate PE in medicine development:

PE activities are now moving towards including science-based patient voices into the medicine development, review, and approval process. I think what happened in the last five years is that, more and more patient groups are becoming more sophisticated, and they understand the drug review processes and their ability in influencing the drug review not just using emotion, also through helping to collect data and sharing therapeutic experiences. ... The cooperation between PHARMA and patients needs also to be built-up in parallel in order to deliver the patients evidence data. [P-06 (PX)]

We talked about patient-driven research, patient-informed research, and patient-engaged research; so, we come to the point that patients are the truly active value drivers in the drug research and development. I think that the better patients can take that leadership, the better the healthcare results could be. [P-09 (PT)]

Patient advocacy organisations use PE to drive research agenda, and work with PHARMA together to see what the assets are both party can bring to the table to establish partnership in the effort to create transparency. … We need to engage all stakeholders in the healthcare system to leverage patients' expertise in living with disease. [P-02 (PX)]

(ii) 'Patient as a partner in regulatory medicine review and approval processes' – an attribute of PE in medicine development at the societal level

At the societal level, interviewees perceived that seeing the patient as a partner in the regulatory medicine review and approval processes is a core attribute of the concept of PE in medicine development, emphasizing shared leadership, partnership and collaboration. Most PE expert interviewees linked this PE attribute at the society level directly with the new VBM paradigm in healthcare and with cross-industry VCC principles. Furthermore, they argued that the notion of the patient as a partner, as a key attribute of PE at the society level, should be applied by all healthcare stakeholders in their interactions with patients, as has been increasingly demonstrated by regulators in their medicine review and approval processes. The following narratives from interviewees support this claim:

PE in medicine development is about involving patients in healthcare decision-making as a stakeholder and partner. [P-24 (PX)]

From a moral perspective, as a society, we have our spend on healthcare, including the investment in medicine development. All the key stakeholders should jointly decide where to spend the healthcare budget, and patients are the most important key stakeholders. We need to design a way to bring patients into the decision-making processes. [P-04 (PX)]

We have these three triangle stakeholders in medicine development – regulators, patients, and PHARMA. In each medicine development, there should be the involvement of these three parties. Patient Organisations are really becoming an official partner in the three-party collaboration which is a top-down driving force for PHARMA to work with patient organisations through PE activities. [P-20 (MD)]

Patients want to be part of the conversation as one important stakeholder sitting with others at the round table as a partner. … Using a patient advisory board in the regulatory review and approval processes allows patients' preferences and PRO data be considered based on scientific evidence. [P-24 (PX)]

Regulators have already involved patients in the benefits-risks-assessment of medicines based on patients' experiences and preference data; further PE in decision-making around drug development is the next steps we are just doing now. [P-04 (PX)]

We have established a 'patient advisors' programme in our organisation, and we will recommend these trained 'patient advisors' participate in the technical panel or

committees at FDA and PHARMA companies to ensure the presence of patients' perspective there. [P-15 (MD)]

I definitely see the shift in medicine development, especially for the regulatory review and approval section, from seeing patients as research subjects, towards searching for meaningful PE and seeing patients as research partners during the medicine development processes. [P-18 (PX)]

For me, PE in medicine development means that patients' voices are taken into careful consideration in the development, review, and reimbursement of pharmaceuticals. It is an ecosystem, now patients' perspectives are being recognised as an important part of this ecosystem. [P-06 (PX)]

Drawing on the above arguments from interviewees, the notion of *the patient as a partner in regulatory medicine review and approval processes* was indicated as a core attribute of PE in medicine development at the society level; it must be present within PE in medicine development due to the impact that regulators can impose in the triangular stakeholder medicine development ecosystem (i.e., regulators, patients and PHARMA*)*.

(iii) '<u>Presence of patients' voices in medicine development</u>' – an attribute of PE in medicine development at the PHARMA level

At the PHARMA level, substantial evidence from the interviews suggested that *presence of patients' voices in medicine development* was perceived by the participants as a key attribute of PE in medicine development at the PHARMA level. A broad spectrum of potential PE activities in medicine development to support the presence of the patient voices was depicted by interviewees, covering (i) joint definition of the research agenda, unmet medical needs, target product profile (TPP), and target population profile at the early

research phase; (ii) joint design of the clinical trial, conducting patient recruitment, gathering patient experience data, conducting benefits-risks-assessment (BRA) at the clinical development phase; and (iii) joint generation of patient-reported outcome (PRO) data, comparative data, real-life evidence data, and long-term usability data at the launch preparation and commercialisation phase. These PE activities suggested by interviewees supported further the core attribute of PE in medicine development: *co-creation through combining the knowledge and experience of PHARMA and patients in interactions* (see ***Figure 9.2*** and ***Annex 9)***. The narratives from interviewees below offer further justification:

> *PE is about engaging patients at the very early stage of research, in order to produce something that is meaningful, relevant, feasible and sustainable.* [P-11 (PX)]

> *At the early stage of drug research, we should ask patients about what it is like to live with a disease, what it is like to take a medical treatment, what their unmet medical needs are, at least including these patients' inputs in the assessment of a new drug's potential which will impact the available treatment options for patients.* [P-04 (PX)]

> *The only reason for PE is that we want to have the right drug coming to the market. … Science-based patient voices play a critical role at all; … if patients' voices become more and more important for the drug review and decisions of regulators, PHARMA will see the importance of having patients' voices data in all steps of the drug development.* [P-06 (PX)]

PHARMA should use two types of PE method in the context of medicine development: (i) consultation, which means to capture patients' inputs on needs and expectations; and (ii) collaboration, which means to engage a small expert patient panel along the medicine development for joint oversight. These two PE methods are complementary to each other, which will ensure that PHARMA has a representative picture of patients' perspectives in the medicine development. [P-16 (PX)]

We need to engage patients much earlier even in the drug discovery phase in terms of setting unmet medical needs from patients' perspective, so the study can already look for outcomes which are important for patients, so that the potential label can already contain information which is patient centric. [P-23 (PX)]

Within PE in medicine development, PHARMA would need to change from an asset-driven scientific-oriented approach to a patient-centric research paradigm. Incorporating patients' experiences in the medicine development processes can ensure matching unmet medical needs of patients with scientific possibilities early on. [P-06 (PX)]

PHARMA should ask themselves in every meeting which research needs to be undertaken, and what does this mean for patients. Put patients first, not at the end. Patient relevance should guide all the discussions about medical needs, impacts, and product quality. [P-01 (MD)]

Using PE to determine what is of most value from the public health perspective to understand what the gaps are for patients. Keeping patients' voices involved to

decide on research priorities and research pipelines – these will be the most impactful actions that PE will bring value to public health. [P-04 (PX)]

It is worth noting that the above narratives from interviewees include a very recent term to describe the core attribute of PE in medicine development at the PHARMA level – i.e., *the presence of patients' voices in medicine development*. This new term, frequently used by interviewees, may be influenced by or borrowed from the PFDD initiative recently launched by the FDA, which emphasizes the need for PE at all stages of medicine development (FDA, 2018b) and, thus, requires the presence of patients' voices to be demonstrated in the submission package by PHARMA for regulatory approval.

Furthermore, the interviewees' perceptions of the relationship between the core attributes of PE in medicine development at different levels were further demonstrated: the meanings of PE from the perspectives of the patient (i.e., *patient as value co-creator*) and society (i.e., *patient as a partner in regulatory review*), have a strong influence on the definition of what PE means within pharmaceutical medicine development (i.e., *the presence of patients' voices*). Following these arguments, the meanings of PE for patients and society offer the purpose and context for PHARMA to define PE in medicine development on the organisational level, because medicine development by PHARMA exists to serve patients and society (du Plessis et al., 2017; Marzorati et al., 2017). The relationship between these PE attributes at the level of the patient, society and PHARMA was strikingly illustrated by one interviewee:

PE starts with the increasing importance of individual patient's experience as a societal driver which translates into the emergence of the patient organisation as collective organised patients, who can influence healthcare policy and PHARMA's

medicine development decisions. … Then, it's like a snowball, the 21st-century cure act mandated FDA using the PE tool and patients' inputs in their review, which tells the PHARMA that health authorities will consider these patients' inputs in their drug review and approval. … So, the avenue that delivering individual patient experience are turned into structured data that can be used to assess the healthcare value to push policy and decision-making, so the idea of partnership between PHARMA and patients to co-develop medicines through PE will determine the long-term reputation and business success of PHARMA. [P-30 (MD)]

As discussed above, drawing on the meanings of PE in medicine development at the levels of patient, society and PHARMA, the core attribute of PE in medicine development as *co-creation through combining the knowledge and experiences of PHARMA and patients in interaction*s was considered justified (see ***Figure 9.2***). This overarching key attribute of PE in medicine development identified from the fieldwork coincides with the findings from the theoretical phase (see ***Figure 8***), which resonate further with the VBM, VCC and SDL theoretical perspectives, adopted in the present study to explore PE in medicine development from a value-creation perspective (see Section 2.5).

5.2.3 *Consequence*: Improved value for patients and all healthcare stakeholders

Consequences are events or incidents that occur as a result of a concept (Walker & Avant, 2014). '*Improved value for patients and all healthcare stakeholders*' was cited by most interviewees as an anticipated core consequence of the concept of PE in medicine development (supported by 23 sources with 123 references in the thematic analysis of interview data). The following three categories identified at the levels of the patient, society and PHARMA led to the development of the core consequence of PE in medicine

development – '*improved value for patients and all healthcare stakeholders'* (see ***Figure 9.3*** and ***Annex 9***):

(i) 'improved patient value for patients' at the patient level (supported by 11 sources with 23 references from interviews);

(ii) 'improved healthcare value for society' at the society level (supported by 10 sources with 21 references from interviews);

(iii) 'improved business value for PHARMA' at the PHARMA level (supported by 21 sources with 78 references from interviews).

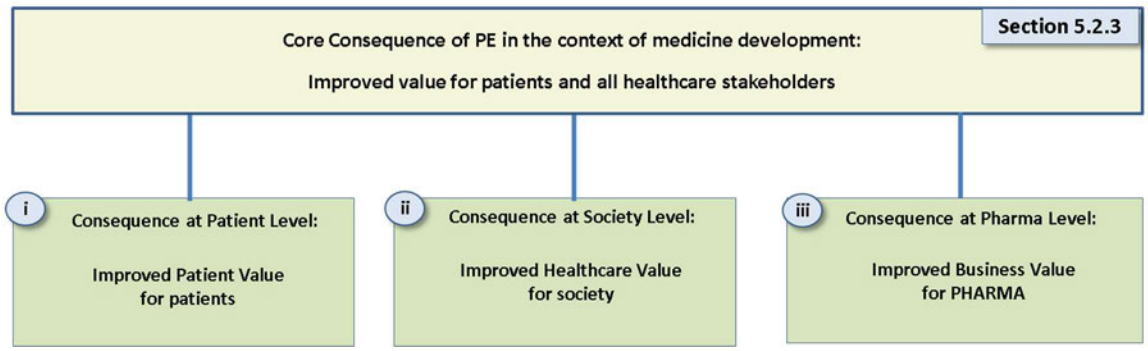

Figure 9.3*: Consequences of PE in medicine development identified from the fieldwork.*

The identified core themes and categories regarding the consequences of PE in medicine development from the fieldwork were closely aligned with the themes identified from the theoretical phase in the present study (see Section 4.2), which are discussed and justified further with the support of narratives from interviewees in the following paragraphs.

***(i) 'Improved patient value for patients'* – a consequence of PE in medicine development at the patient level**

Improved patient value (i.e., improved health outcomes and positive patient experiences) was attested by most interviewees to be an anticipated primary positive consequence of PE in medicine development at the patient level. This claim assumed that PE in medicine development can lead to the development of improved medicines by PHARMA through better fulfilling the expectations and needs of patients, thus contributing

to better health outcomes of patients. However, patients' voices were still considered to be the missing piece in the current, conventional medicine development process where patients were involved as study subjects without a voice. The lack of the patient voices in medicine development processes was argued by interviewees to carry a risk that the medicines developed by PHARMA may not meet patients' needs even though they may make sense in scientific terms. Therefore, integrating patients' voices into the medicine development processes within PE was considered by participants to be important in filling this gap, linking the patients' value proposition with PHARMA's product offerings to improve patient outcomes and satisfaction, thus entailing *improved patient value* as a primary consequence of PE in medicine development. Narratives from the interviewees offer further insights and justification for this claim:

> *PHARMA's current approach is to search for molecules and purpose them for certain disease areas. If they can put patients' needs and hopes involved in considering what needs to be developed, and what is the most value from the public health perspectives to fill the gaps for patients, and then decide on the research priorities and pipeline. In my mind, this is the single most impactful action that PE will bring value for patients and public health.* [P-04 (PX)]

> *I think patients' inputs can help the PHARMA to develop better medications to fulfil the expectations and needs of patients better. E.g., the size of the medicine, the right formulation, treatment intervals and regimen, as well as patients' perspectives regarding the safety and efficacy profile of the medicine.* [P-15 (MD)]

> *I am really convinced that usability from patients' perspectives is super-important for medication compliance which has a huge impact on the efficacy of medicines. ...*

PHARMA cannot offer improved usability if they do not understand the needs and daily life of patients. ... PE is therefore essential in this context to optimise the usage of medicinal products through observation, shadowing and interacting with patients in real settings, in order to optimize the interfaces, usability and experiences for patients within the technical approval. [P-03 (PT)]

For me, PE is about how to improve the patients' outcomes – that is the only goal here. I don't think there is disagreement that more robust, scientific patients' voices data will drive positive outcomes, that's why PE needs to be encouraged. [P-06 (PX)]

Greater PE will produce better research – more targeted research. It may not necessarily reduce costs, but it makes all the research more relevant for patients and may produce a better health outcome record, so everyone has potentially a benefit in that. [P-07 (PT)]

From the above discussions, '*improved patient value - a consequence of PE in medicine development at the patient level*' was suggested both by the interviewees and literature findings (see Section 4.2). Furthermore, patient value was identified as a key related concept to PE in medicine development based on the thematic analysis of the interviews. In this context, patient value was described by interviewees as:

Positive health outcomes associated with an effective and safe medicinal product and treatment that have fulfilled patients' needs and expectations and delivered a positive patient experience. ([P-03 (PT)]; [P-04 (PX)]; [P-15 (MD)] – see above quotations)

The meaning of patient value derived from the fieldwork as described above differs slightly from the definition of patient value offered in the literature, which refers to '*the unique preferences, expectations and experiences of individual patients towards medicinal product and treatment*') (see Section 4.4 and ***Table 9***). Nevertheless, both definitions point to the common components of health outcomes, expectations, needs and experiences of patients, and the expectation that these will be addressed and fulfilled through PE in medicine development. As a result, *improved patient value* was justified as an expected consequence of PE in medicine development at the patient level from both the literature and the fieldwork. The relevance and significance of the concept of patient value in relation to the concept of PE in medicine development were elaborated by interviewees as follows:

> *I am convinced that usability from patients' perspective is super-important to determine patient experience and has a big impact on the compliance and efficacy data of the medicine.* [P-03 (PT)]

> *I think a big benefit of PE could be innovation, if we use a human-centric design approach throughout the drug development processes to develop a medicine that patients want to take.* [P-04 (PX)]

> *I think if the PHARMA company is only interested in putting PE on their marketing brochure – it's an obvious public relations effect, whereas a company interested in improving the real outcomes for patients will follow a genuine PE approach.* [P-12 (PT)]

PE is about addressing patients' needs in a more effective way with the objective to have more effective medicines covering more patients' needs under certain conditions; ... In order to fulfil this objective, you can't do it without PE. [P-32 (PX)]

The above interviewees underlined that PE is all about understanding and delivering improved patient value through a better understanding of patients' needs in medicine development, which is expected to lead to improved health outcomes. However, despite a wide consensus regarding this assumed positive consequence of PE in medicine development at the patient level, little empirically measured data can be found to substantiate this association, either in the literature or in the interviews. Interviewees suggested that understandings about *what* and *how* of PE in medicine development should be made clear prior to the proper PE conduct and measurement of the consequences. Interviewees addressed this fundamental issue in the understanding of PE in medicine development as follows:

The fundamental question is what PE is, what patients' voices are acceptable and with which rigour to be acceptable. I think these are issues to be addressed surrounding the PE before we can measure. But we are not there yet. [P-17 (PT)]

I would say that most companies do understand what the value of PE is, although sometimes they do not necessarily know how to implement the PE company-wide. They are also very aware about they need to be compliant with regulations regarding PE to run their business. So, PE is really not an easy concept which is much complex and difficult to build into all the processes of medicine development. [P-28 (PX)]

> *From my point of view, we need to be clear about the level and the nature regarding PE. What the PE is about? Is it about PE in an organisation, or about public policy? We need to understand the clear nature of PE before we can discuss it in detail, because PE as a term is very vague.* [P-32 (PX)]

Drawing on the insights from the interviewees, a clear understanding of PE in medicine development is a prerequisite for future empirical measurement of this concept and testing the correlations of these PE components. In this regard, the present study will offer an original contribution to the body of knowledge through developing a PE conceptual framework in medicine development (RO3, see Section 6.3) as foundational work for the further development and measurement of this concept in the future.

(ii) 'Improved healthcare value for society' - a consequence of PE in medicine development at the society level

From a societal perspective, most interviewees perceived that PE in medicine development would allow the disease areas with the highest unmet medical need to be addressed at a societal level, thus facilitating the development of better medicines to address these unmet medical needs and improving healthcare value for society. Healthcare value – as a key related concept to PE in medicine development – is defined as '*positive results in collective patients' outcomes, safety and satisfaction at a reasonably affordable cost, in association with a medicinal product and/or treatment*' (see Section 4.4 and ***Table 9***). This assumed positive consequence associated with PE in medicine development at the societal level concurred with the findings from the theoretical phase (see Section 4.2). Several relevant aspects supporting this claim are illustrated below by the interviewees:

PE in medicine development provides in-depth understandings regarding the socio-psychological effect and disease management experiences associated with medical treatments from patients' perspectives, which allows developing measurement metrics which are highly relevant for patients.… PHARMA used to measure biomarkers for different conditions – a kind of black and white easy measurement. Measuring social factors such as self-efficacy and self-agency associated with PE is a bit fussier, which are however very important for patients to inform a better clinical study design. [P-29 (PT)]

From the society perspective, PE can improve the healthcare and medications for patients – paediatric patients in particular, because lots of paediatric diseases are treated off-label; PE in medicine development can gain more knowledge about clinical trials, the role of patients, and make progress in this area. [P-32 (PX)]

I define the healthcare efficiency as to have the right drug to the right patient with the right dose at the right time. I think patients' voices in terms of PE are absolutely appropriate to expedite that proposition. [P-06 (PX)]

There has been a series of empirical research which demonstrated that if you get patients engaged in management of their own disease, you will have better outcomes. ... PE in the context of medicine development allows PHARMA to develop medicines addressing the gaps from patients and public health perspectives, which will bring impactful value to the society. [P-04 (PX)]

Thus, insights gathered from the interviewees in the present study offered strong arguments and empirical support for the claim that *improved healthcare value* is an expected

consequence associated with PE in medicine development at the society level. This claim assumes that PE in medicine development would allow the development of better and more effective medicines, which meet hitherto unmet medical needs and patient expectations and improve the patient experience, thus improving healthcare value as collective positive health outcomes on a societal level.

(iii) 'Improved business value for PHARMA' – a consequence of PE in medicine development at the PHARMA level

Most interviewees argued that there are many benefits associated with PE in the context of medicine development at the PHARMA level, from both the operational and strategic perspectives, including:

(i) PE can support better design in the target product profile (TPP) of medicines through matching the unmet medical needs of patients and society in early research phases, allowing early risk mitigations of trial failure:

PE allows innovation following a human-centric design approach to develop a medicinal product that patients want to take. [P-04 (PX)]

(ii) PE can support better clinical trial design and improved operational outcomes:

In the clinical trial design, for the development of target product profile, which is intended to be brought to the market, you should also think about what are the target patient profile, and what are patients looking at the TPP and get patients' inputs through PE before the trials even happen. [P-05 (PX)]

(iii) PE can support regulatory approval and faster time-to-market and commercialisation:

It is a good thing that health authorities also consider patients' inputs as another important factor beyond efficacy and safety data in the submission package, so the presence of patients' voices through PE will be an important value-adding differentiation factor to support regulatory approval and market uptake. [P-15 (MD)]

(iv) PE can lead to improved trust and long-term reputational benefits:

From a reputation perspective, the benefit is huge associated with PE for PHARMA in terms of branding and trust – to establish an image as a trust-worthy company due to engaging patients in the long run. The trust gained through joint development of medicine is huge. I think those are intangible ROI associated with PE, although you may see the effectiveness of the company started to evolve over time. [P-12 (PT)]

(v) PE can bring improved outcomes for patients and healthcare which will lead to improved ROI and the business success of PHARMA*:*

PE will help PHARMA to produce something relevant and meaningful that patients more likely to take up in a sustainable way; and it is good for their reputation and patients' experience, which will help PHARMA to fulfil both their social responsibility and financial meaningfulness. That is why PE is so important for the long-term success of PHARMA. [P-11 (PX)]

Furthermore, interviewees suggested that improved patient value at the patient level, associated with PE in medicine development, will lead to improved healthcare value at the

societal level. These two key success indicators of a medicinal product could lead to improved business value for a PHARMA company consequently:

> *If PHARMA does the PE right, the consequence will be that the product developed is more likely to improve patients' outcomes, so the product will get to the market faster, generate more healthcare benefits and therefore more revenue for PHARMA. … PE can serve also as a good-will trust-building between PHARMA and patients, for the PHARMA industry to demonstrate themselves on a global scale as an honest, transparent and trustworthy partner through authentic PE, which will link to the commercial success of the PHARMA in the long-run.* [P-02 (PX)]

> *I think these PE activities are win-win for both patients, society, and PHARMA. If we can get patients' feedback that the new medicine can improve their health outcomes, and the comparison with the current standard of care also demonstrate improved healthcare value from the societal perspective, this will ultimately benefit PHARMA as well; because PHARMA has the social responsibility to develop meaningful medicines for patients and public health besides the financial meaningfulness for PHARMA.* [P-15 (MD)]

> *I think PE will benefit PHARMA in two aspects: (i) operational value in terms of better study design, faster patient recruitment, less drop-outs and less protocol amendment, and allow quicker decision-making – these are very tangible operational values you can put dollar signs on; and (ii) I think the harder, but long-term, intangible value is the trust and reputation gains through PE in the long run, which*

is hardly to put a dollar sign on, but long-term reputational benefits associated with PE is a hugely valuable intangible asset for PHARMA. [P-27 (MD)]

The insights gained from the interviewees regarding the consequences of PE in medicine development at the PHARMA level are in alignment with the theoretical perspectives based on SDL, VCC and VBM, as they all claim that value is always determined by and co-created with the customers (Prahalad & Ramaswamy, 2004; Vargo & Lusch, 2004) and that value should be defined and measured around the patients as the beneficiaries of healthcare and medicines, which should determine the rewards for all actors in the healthcare system (Brown et. al., 2005; Porter, 2010) (see Section 2.5). Insights gained from the interviewees supporting these theoretical claims are offered below for further justification:

I think the ultimate value associated with PE is that the medicine the PHARMA company put on the market will meet the patients' needs and therefore they will do their business well. ... PHARMA wants to be perceived by patients, consumers and public as patient-centred companies for reputation reasons and to increase the trust – these are intangible benefits of PE but related to the ROI the company wants to achieve. [P-28 (PX)]

We have created a financial model to calculate the financial benefits associated with PE initiatives including time-to-market, cost, and quality of clinical trials; ... In order to facilitate PE in PHARMA, you need to frame it and link it to the commercial aims of the company. [P-02 (PX)]

I think one of the major benefits, although we are still far away from this, is really to have the best medicine developed for the patients. … I think PE is also a measure of trust in the industry; since we all hear from the public news saying that the PHARMA is only looking at the money, not really looking at the patients. With this close connection through PE between PHARMA and patients, we will have better understandings from both sides – we understand the patients' needs and also the patients can get a better understanding about what the medicines can do for them. I think this is a little step on the road to increasing the trust of patients in PHARMA. [P-19 (MD)]

The above narratives from interviewees suggested that delivering improved patient value and healthcare value within PE in medicine development will reward PHARMA in both operational gains and long-term strategic success. Furthermore, these consequences of PE in medicine development found at the PHARMA level endorsed the findings derived from the theoretical phase (see Section 4.2). Nevertheless, there is still a lack of empirical testing for the claims for improved value associated with PE in medicine development. This was considered as a knowledge gap that warrants further research (see also discussion in Section 4.3), as illustrated by one interviewee below:

I think there should be some parameters defined to measure the PE value for the PHARMA's business, in order to generate evidence to support PE in drug research and development. [P-05 (PX)]

5.2.4 *Barrier*: Value discrepancy, challenges in methodology, process and culture

Following the evolutionary concept development approach, concepts are seen as dynamic and can be only interpreted with a multitude of contextual factors, such as barriers

and facilitators associated with the use of a concept in practical settings (Rodgers, 1989). Considering these aspects, interviewees were asked to describe the barriers that they believed might prevent the effective application of the concept of PE in medicine development practices. Information gathered from the fieldwork regarding the barriers to PE in medicine development can offer valuable insight about the contextual issues that need to be addressed to further advance the effective application of PE in medicine development practices.

Several barriers to the concept of PE in medicine development were identified by the interviewees at the level of the patient, society and PHARMA as follows (see ***Figure 9.4*** and ***Annex 9***):

(i) patients' health literacy, capacity and maturity of POs, at the patient level (supported by 12 sources with 24 references in the thematic analysis of interview data);

(ii) HCP paternalism, lack of aligned PE framework including methodology and processes, at the society level (supported by 19 sources with 55 references in the thematic analysis of interview data);

(iii) PHARMA's cultural resistance, tokenism, mistrust and disconnect with patients, at the PHARMA level (supported by 28 sources with 154 references in the thematic analysis of interview data).

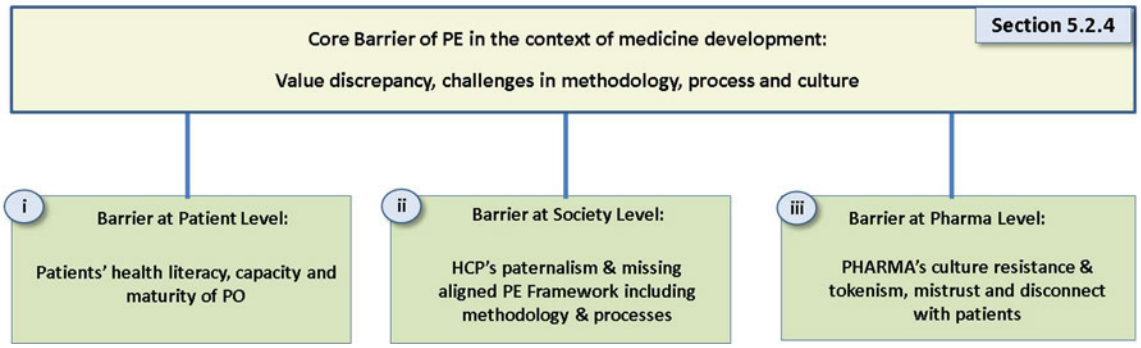

Figure 9.4*: Barriers to PE in medicine development identified from the fieldwork.*

Furthermore, interviewees suggested that these identified barriers to the concept of PE in medicine development at different levels could largely be attributed to the '*value discrepancy between healthcare stakeholders and the challenges in methodology, processes and culture'* associated with PE in medicine development (supported by 30 sources with 228 references in the thematic analysis of interview data). These are the most critical barriers suggested by interviewees and need to be addressed to facilitate the acceptance and establishment of PE in medicine development practices. These critical barriers to PE in medicine development were illustrated by interviewees as follows:

> *The healthcare system is fragmented and not designed around the patients; …a whole host of factors need to converge to get patients really engaged in the medicine development. … Qualitative research methods are usually used in these studies to capture patients' perspectives which are often dismissed by the R&D folks as less rigorous. I think we need to combat by stressing that different research methods are appropriate in different situations for different research questions – they both have scientific rigour – including the 'patient voices type of research'. … Sometimes this kind of qualitative data are perplexing for the biology scientists.* [P-04 (PX)]

> *Some PHARMA and regulators used to think that patients' voices aren't really science-based and refuse to include these patients' voices data into the product review package. … So, the intent of PE is to gather scientific-based patient input data by public health to make sure the drug is developed in the right way, approved in the right way, used, and reimbursed in the right way to improve patients' outcome.* [P-06 (PX)]

The two interviewees above referred to the methodological challenges in integrating qualitative patient voice data in a biomedical world dominated by quantitative statistical data, such as medicine development. Value-loaded data from the patients' perspective were often regarded as less rigorous and 'perplexing' for medicine developers and regulators. As such, PE needs to overcome the dominant positivist ontological stance in the biomedical field and find the right method to integrate patient value with scientific evidence, following a value-creation perspective. The methodological challenges associated with value discrepancy among stakeholders, as a barrier to PE in medicine development, were further elaborated by one interviewee as follows:

> *I do not think that PHARMA has understood the potential of PE and utilised it in a right way now. ... The target product profile of a medicinal product is pretty much shaped by the molecule defined by the science. The scientists might have a deep sense of what kind of outcome measures they are looking for, ... it does not really involve understanding and capturing patients' insight into the science and the product potential any way. ... Most R&D people see PE as a burden as opposed to seeing it as an opportunity.* [P-10 (PT)]

This interviewee described the value discrepancy among healthcare stakeholders as a key barrier to PE in medicine development. Research scientists in PHARMA design the target product profile of a medicinal product based on scientific evidence, while patients' expectations of a therapy are expressed in relation to its impact on their HRQoL (Boudes et al., 2018). Thus, the underlying value discrepancy among healthcare stakeholders needs to be aligned prior to the development of a PE methodology, to overcome these identified barriers (Kelly et al., 2015).

The identified barriers to PE in medicine development at different levels are further discussed and justified in the following paragraphs. Narratives from interviewees are quoted to allow rich and deep insights with a focus on depicting rationales and implications.

(i) 'Patient's health literacy, capacity and maturity of PO' – a barrier to PE in medicine development at the patient level

At the patient level, patients' health literacy and capacity to collaborate with HCPs (including PHARMA) were frequently mentioned by interviewees as key barriers to PE in medicine development at the patient level. Specifically:

(a) medicine development is a highly regulated and specialised field, and it may not be easy for lay patients without medical education to understand this field for PE activities:

For patients to participate in medicine development decisions, they would need a big training to understand the medicine development processes to be able to engage with researchers for these discussions. [P-18 (PX)]

(b) the power imbalance between HCPs (including PHARMA) and patients was still considered relevant with regards to communication and information access:

The doctors will prescribe medicine, and the patients normally do not have any medicine knowledge, sometimes they even did not understand what kind of disease they have, and what kind of medicines they should take. They just trust what the doctors said. I think this is the major reasons why the patients are not treated as customer, because doctors are the king who has the power over patients. [P-08 (MD)]

(c) patients may think about what they want instead of what they need; this 'wishful thinking' by patients could be considered meaningless and irritating by HCPs within PE in the context of medicine development:

Some patients could be incredibly annoying, they do not think about what they need but what they want. It could be a language barrier too – these are barriers to PE *on the individual patient level.* [P-07 (PT)]

Furthermore, it became clear from the interviews that, at the patient level, patients' health literacy and ability to express their expectations and needs both on the individual and aggregate level were critical for impactful PE in the context of medicine development. These abilities are, however, not yet fully established at the patient level:

Patients surely need some training to be engaged in the medicine development, so that the interaction dynamics through PE are fair, and patients do not feel the power imbalance disadvantageous for them. If patients are going to participate in the Go/No-Go decisions about medicine development through PE, they would need a big training to understand the medicine development processes to be able to engage with researchers for these discussions. [P-18 (PX)]

Additionally, interviewees suggested that POs have an important role to play in, for example, offering training to patients to understand medicine development processes, setting up patient research networks, and interacting with other healthcare stakeholders as competent and organised partners. POs are becoming an increasingly important stakeholder, representing patients in the context of medicine development, through the advancement of PE in medicine development over recent years, as illustrated by interviewees:

Patient organisations are increasingly representing patients within PE in medicine development. However, POs are not equally developed – some are more sophisticated and well-funded, others are very small. POs need to set up infrastructure, foundations, and meaningful capacity in order to engage meaningfully with PHARMA in the drug development. [P-10 (PT)]

Patient organisations are growing and some of them are very active, such as in Parkinson's disease. It depends on the disease area; most of the POs are just offering some basic support to each other, they are by far not involved in the research and development of medicine yet. They lack the capacity and influence yet to be a research partner. [P-17 (PT)]

Patient organisations are becoming more and more self-organised, e.g., in Europe, a huge umbrella PO under the European Patient Forum (EPF) including 700 regional and local patient groups are evolving, and they are continuing to build up capacity for PE purposes. [P-05 (PX)]

The PE barriers described above at the patient level could be partially explained by the fact that PE in medicine development is an emerging social phenomenon (Lowe et al., 2016). Patients are now expected to take an active role to contribute towards medicine development, but the PE method and processes are still evolving and not yet defined (Smith et al., 2016). While it is acknowledged that it is challenging for a lay patient without a medical education background to co-develop medicines together with PHARMA R&D teams, there is increasing evidence that patients have started to organize themselves through

POs and to build up their health literacy and capacity collectively, in order to fulfil their new active role within PE in medicine development, as illustrated by an interviewee from a large PO from the USA:

> *We [the National Health Council – the biggest independent umbrella patient organisation in the USA] offered training to patients and communities to build up their capacity to advocate themselves; and we also train patients to understand research and the impact of research on public health and to enable them to step in as co-investigators, stakeholder engagement advisors. … We want to have the most educated patient research communities in terms of capacity building to participate in PE activities.* [P-02 (PX)]

It was further suggested in the literature that the more educated and competent the patients are, for PE in medicine development, the more seriously their inputs and voices are taken and valued by HCPs (including regulators and PHARMA) (Brett et al., 2014; Carroll et al., 2017; Pitts, 2016). Therefore, the perceived barrier at the patient level (i.e. *patients' health literacy, capacity and maturity of PO*) is closely related to the other identified barriers (i.e., *methodology and process barriers at the societal level*, and *PHARMA's culture resistance, tokenism, mistrust and disconnect with patients at the PHARMA level*), since all these barriers were suggested to be rooted in the value discrepancy associated with medicine development among stakeholders (Bae, 2015; Bloom et al., 2018; Marzorati & Pravettoni, 2017). In particular, value discrepancy as a barrier to PE in medicine development was suggested to be deeply rooted in the paternalist attitude of HCPs (particularly at the PHARMA level) who believe that non-experts (such as patients and lay service-users) have little or nothing to contribute to medicine development which, conventionally, is the sole

domain of HCPs with high levels of professionalisation and specialisation (Burns et al., 2014), as illustrated by interviewees:

> *We are talking about a company's culture and underlying value system which dictates how patients are viewed.* [P-28 (PX)]

> *PE is about willingness to share control, and people might fear loss of control in the sharing process within PE. … Especially when PHARMA researchers have done medicine development on an academic and scientific level for 20–30 years, they may be not used to share the control. … PHARMA needs to demonstrate authentic messaging that they desire to improve public health, not only do the PE for the sake of profit.* [P-02 ((PX)]

Taking the above arguments into account, the perceived barrier at the patient level (i.e., *patients' health literacy, capacity and maturity of PO*) is attributable to the value discrepancy between healthcare stakeholders, because different values pursued by stakeholders underpin different priorities and different ethical judgements (Bae, 2015; Kelly et al., 2015). In particular, PHARMA needs to appreciate patient value in order to acknowledge the patient as a value co-creator in medicine development, which has often been described as a missing piece within PE in medicine development (Miseta, 2015a; Robinson, 2013; Sartori et al., 2016; Sharma, 2017).

(ii) 'HCP's paternalism, lack of an aligned PE framework including methodology and processes' – a barrier to PE in medicine development at the society level

Interviewees suggested that PE in medicine development is still evolving slowly, despite the wide consensus that it is the right thing to do. Interviewees offered their

perceptions about *HCP's paternalism and the lack of an aligned PE framework including methodology and processes,* which was argued to be currently a major barrier to the concept of PE in medicine development at the society level. In-depth illustrations of these barriers to the concept of PE in medicine development at the society level were provided by interviewees in several respects:

(a) the predominance of a paternalist approach on the part of HCPs in healthcare and medicine development:

> *One big issue is that HCPs are trained in a way that they believe that they know everything about caring of patients in a paternalist approach. I think that physicians working in the R&D function of a PHARMA company bring this paternalist position with them, so they believe that they know patients, they know what the patients need, and patients are just lucky to pick up their drugs and should be grateful because physicians know better how to develop the drugs for patients. So, I think this mindset is encoded already in their medical training as a physician, which underlines the whole effort for PE to be embraced.* [P-04 (PX)]

> *There are many barriers making the PE does not work. The attitude of HCP could be a big hurdle for them to appreciate the patients' inputs and take time to talk to patients.* [P-07 (PT)]

> *Regarding culture change, the R&D team may still not understand why PE is a good idea and they do not believe there will be any return on investment associated with the PE activities, and they want to maintain the way they have done in the past regarding medicine development.* [P-26 (PT)]

(b) the discrepancy in value understandings (such as efficacy and safety from a HA perspective versus cost-effectiveness from an HTA perspective and patient experience from a patient perspective) in the context of medicine development; the current healthcare system is not designed around patients:

> *The current clinical study practices in drug development of PHARMA are based on the interactions with investigators (HCPs), we do not have established collaboration with patient organisations yet, which is also due to legal constraints when contacting patients. So, PHARMA is used to sticking to established practices following the legal regulations, which are major hurdles for PE uptake in medicine development.* [P-19 (MD)]

(c) the questions of 'how' in PE in medicine development are still to be answered with regards to methodology, processes, and culture change. This issue requires an aligned PE framework to be designed in the context of medicine development with the involvement of all healthcare stakeholders (i.e., regulators, patients, and PHARMA):

> *I think the other challenge associated with PE is the missing of a solid framework; we need more examples of how PE can be done well within the solid framework and demonstrate the value of it.* [P-14 (PT)]

> *I think that people working on policy should discuss how the patients' voices are being used in the medicine development in a right way; and how real-world evidence is going to be used and how we, as patient organisations, can contribute to this work; and how patients' voices should be included in the*

> *regulatory package in a rigorous way and how the regulators interpret it.* [P-17 (PT)]

> *For PHARMA, the biggest challenge is to figure out how to do PE in an authentic way and not only do it for the profit which strikes to the PHARMA. Some bad cases in the PHARMA industry can put bad reputation on the whole industry, which formed the perception that PHARMA does not really care about patients but only to satisfy their bottom-line.* [P-02 (PX)]

Drawing on the above discussions, the barriers to PE in medicine development can largely be attributed to the underlying *value discrepancy among healthcare stakeholders and lack of an aligned PE framework, including methodology and processes*, for PE in medicine development. This was indicated as a major barrier to PE in medicine development at the society level in both the literature and the interviews (see ***Table 7.1*** and ***Figure 9.4***).

(iii) 'PHARMA's culture resistance, tokenism, mistrust, and disconnect with patients' – a barrier to PE in medicine development at the PHARMA level

Multiple factors for the resistance of PHARMA to the concept of PE in medicine development were discussed by interviewees. *PHARMA's culture resistance, tokenism, mistrust and disconnect with patients* were suggested as key barriers to PE in medicine development at the PHARMA level (supported by 28 sources with 147 references in the thematic analysis of interview data). Interviewees offered in-depth illustrations of these barriers, preventing PHARMA from pursuing authentic PE in medicine development:

(a) PHARMA's culture resistance, tokenism and mindset inertia and disconnect with patients:

It is especially difficult to convince the physicians about the value of PE. They will say - I am medically trained for cardiovascular disease, why should I ask patients about this disease after having worked on the cardiovascular disease for 20 years. [P-20 (MD)]

PE is about willingness to share control and people might fear loss of control in the sharing process within PE; that is a challenging thing, especially when you have done medicine development on an academic and scientific level for 20–30 years, you may be not used to sharing control. [P-02 (PX)]

Most PHARMA scientists see PE as a burden as opposed to seeing it as an opportunity. The way PHARMA is approaching PE so far is a PR victory and window-dressing activities. [P-10 (PT)]

(b) 'don't know how' – challenges regarding methodology, processes, mechanism and the PE contribution to business success:

Patients can provide information about the complex experiences and nuances of living with a disease, there are some treatment avenues the researchers may never ever have thought about without capturing patients' perspectives. [P-12 (PT)]

There are many hurdles to PE on the PHARMA side: cost is one of them, and cultural resistance is the other one; parallel to these is the lack of credible empirical evidence of the positive impacts of doing PE in medicine development. [P-18 (PX)]

I think there was little value just listening to patients without quantifying these inputs in a meaningful way. In order to get advantages of this broader patients' perspectives, PHARMA needs profound methodology to gather and analyse these patients' data. [P-12 (PT)]

Most PHARMAs do understand the value of PE, although sometimes they do not necessarily know how to implement PE in their company; PE is really not an easy concept which is much complex and difficult to build into the established processes of medicine development. [P-28(PX)]

(c) PHARMA is perceived as science-driven over delivering patient value:

PHARMA still considers regulators and prescribers as customers and sees patients as passive recipients for the medicines, although that has gradually changed, and shared decision-making of patients and physicians has evolved. [P-27(MD)]

For biomedical researchers, who are often not trained to use qualitative data in their research, it could be very alarming to see these PE-related data being used for decision-making and conclusion. [P-05 (PX)]

Taking the above discussions into account, the key barriers to PE in medicine development at the PHARMA level was suggested by the interviewees to be *PHARMA's culture resistance, tokenism, mistrust and disconnect with patients*. These aspects were criticized by interviewees and depicted as a major hurdle for PHARMA to pursue authentic PE in medicine development to serve patients. PHARMA's cultural resistance can again be attributed to the *value discrepancy between healthcare stakeholders* regarding PE in

medicine development because different value perspectives dictate the priorities and ethical judgements (Marzorati & Pravettoni, 2017; Perfetto et al., 2017). Considering the above arguments, *value discrepancy and challenges in methodology, process and culture* were identified as overarching key barriers to the concept of PE in medicine development (see ***Figure 9.4)***, as substantiated from both the interviews and the literature.

The insights generated from the interviews concerning the barriers to PE in medicine development offered an in-depth understanding about the current use of this concept in practice. These identified barriers revealed further how receptive users are to this concept and what need to be done to advance the concept in practice. These are important elements in the further development of the concept. Accordingly, facilitators for the concept of PE in medicine development were identified, based on the interviews, that is, influencing factors that might help to overcome the PE barriers identified and promote the wider establishment of the concept of PE in medicine development practices. Facilitating actions for PE in medicine development identified from the interviews are presented and justified in the next section.

5.2.5 *Facilitator*: Develop aligned PE framework in medicine development

Corresponding to the barriers to PE in medicine development described above, the interviewees also discussed facilitating actions which may help to overcome the barriers. These facilitators to promote PE in medicine development at the levels of the patient, society and PHARMA are categorized as follows (see ***Figure 9.5*** and ***Annex 9***):

(i) at the patient level, the 'engagement of the right patients with the right purpose' was indicated by interviewees to be a key facilitator of the concept of PE in medicine development (supported by 16 sources with 39 references through thematic analysis of interview data);

(ii) at the society level, 'developing a multiple-stakeholder-aligned PE methodology and processes framework' was suggested as a key facilitator for PE by participants at the society level (supported by 16 sources with 35 references through thematic analysis of interview data);

(iii) at the PHARMA level, 'PHARMA to integrate patients' voices in medicine development' was argued as a key facilitator for the concept of PE in medicine development (supported by 24 sources with 64 references through thematic analysis of interview data).

A further thematic analysis across the interview dataset from all stakeholders revealed an overarching core theme: '*develop aligned PE framework with multi-stakeholders along the medicine development lifecycle*', which was regarded as an overarching key facilitator to PE in medicine development (supported by 28 sources with 140 references through thematic analysis of interviews). These identified facilitators for PE in medicine development are discussed and justified further in the following paragraphs.

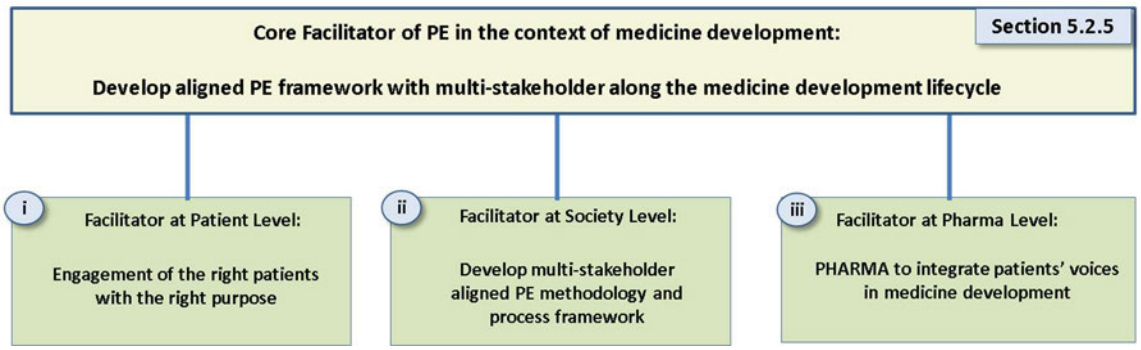

***Figure 9.5**: Facilitators for PE in medicine development identified from the fieldwork.*

(i) '<u>Engagement of the right patients with the right purpose</u>' – a facilitator to PE in medicine development at the patient level

Interviewees argued that patients' anecdotes are of little help when incorporating the patient voices into the medicine development processes. Rather, engaging patients systematically to gather the right input for the right purpose with scientific rigour, will

facilitate the establishment of PE in medicine development at the patient level. PE might serve different purposes at different stages along the medicine development life cycle and therefore requires the engagement of the right patients with the right purpose at the patient level. One interviewee elaborated this facilitator as follows:

> *You can involve patients and PO at every stage of medicine development; the patients can develop a kind of ownership of the products through this involvement process. … But the question of who the right patients are to be involved depends on what you are looking for. There are different patients there who can provide different inputs depending on your research purposes.* [P-16 (PX)]

For consultation purpose with a view to informing clinical study design and conducts, it was considered by interviewees as appropriate to engage a large, diverse, and representative group of patients. Conversely, for collaboration purpose in terms of oversight and joint decision-making throughout the medicine development life cycle, interviewees suggested involving a handful of patient advocates or expert patients (i.e., patients who have particular knowledge, expertise, network and the capacity to speak on behalf of a large group of the patient community). These expert patients can serve on patient advisory boards or patient panels, sitting at the table together with PHARMA medicine developers and regulators, as illustrated by some interviewees:

> *For patients to participate in Go/No-Go decisions, they need a big training to understand the medicine development processes to be able to engage with the researchers for these discussions – they are 'expert patients'; whereas for the other* PE *activities in medicine development they don't need training and they just need to*

bring their experiences of living with disorders with them, as naïve patients. [P-18 (PX)]

Expert patients are valuable, which is emerging with the further development of different patient organisations, but we need also real patients under the disease condition who can provide real-life disease experiences what we are looking for. We need a mixture of these naïve patients and their caregivers to capture their disease burden experiences. [P-07 (PT)]

Logically, for different PE purposes in the context of medicine development – such as consultation or collaboration, different patient populations with different profiles – such as normal patients and their care-givers; or expert patients – are required to fulfil specific purposes. Consequently, the *engagement of the right patients with the right purpose* was suggested as a key facilitator to PE in medicine development at the patient level. Narratives from interviewees are provided below for further justification of this claim:

In UK, the regulators do invite two patients with relevant conditions to participate in the drug review meetings. What I do not find helpful is that these patients produce soft stories about their disease and argue how the new drug can make their life better. Rather, what is helpful is that patient organisations have data to articulate how the disease impacts the lives of their members, how many of them are suffering from the disease burden. Whenever the PO comes to the PHARMA with solid data, it is helpful; the single, sad patient story is emotional, but it does not help to make decisions. [P-27 (MD)]

It depends on what part of the drug development processes you are talking about. For example, we are including some small qualitative studies with focus groups and individual interviews with patients and include these data in our structured benefit-risk-assessment that goes into the clinical overview. In terms of patient selection, we try to get a representative sample which reflects the key characteristics of that target patient population. [P-04 (PX)]

I think this kind of 'patient-voice type of research' is not quite understood, especially this qualitative research is often dismissed by the R&D as less rigorous than quantitative research. I think we need to combat this by stressing that different research methods are appropriate in different situations for different research questions – they both have scientific rigour. [P-04 (PX)]

Drawing on the above arguments from the interviewees, *engagement of the right patients with the right purpose* (such as engaging normal patients and their care-givers for consultation purpose, while engaging expert patients for collaboration purpose) was considered to be a key facilitator for PE in medicine development at the patient level, and this aligned with the findings derived from the theoretical phase (see ***Table 7.2***).

(ii) 'Develop multi-stakeholder-aligned PE methodology and process framework' – a facilitator for PE in medicine development at the society level

At the society level, the lack of an aligned PE methodology and process framework, endorsed by all healthcare stakeholders, was confirmed by the majority of interviewees as the key hurdle to overcome in order to facilitate PE in medicine development (see discussion in Section 5.3.4 and ***Figure 9.4***). The concept of PE in medicine development was considered by interviewees to be an emerging new science which has challenged the

established, conventional medicine development approach. However, the PE foundations – a common understanding regarding PE meanings, methodology and processes – are to be developed and integrated into the existing medicine development life cycle based on an aligned value commitment among healthcare stakeholders. Interviewees elaborated on this critical facilitator for PE in medicine development at the society level as follows:

> *PE space is multi-dimensional which needs to be tackled from different angles. With patients' voices being evolved and successful, it should be good for everybody – patients, PHARMA, regulators and HTA bodies. If everyone has something to win through PE in this regard, PE will evolve and move forward.* [P-06 (PX)]

> *The Council for International Organisation of Medical Science (CIOMS) and WHO have recently established a new working group, aiming to put some guidance on how to incorporate patients' inputs into the medicine development processes. We are trying to build up a global approach for* PE *worldwide.* [P-06 (PX)]

Here, it became evident that this recommended facilitator for the concept of PE in medicine development ('*Develop multi-stakeholder-aligned PE methodology and process framework*') relies on alignment among healthcare stakeholders regarding PE methodology and processes at the society level. This insight concurred with the findings of the literature analysis in the theoretical phase (see Section 4.3.1 and ***Table 7.1***). Furthermore, interviewees emphasized the importance of putting patient value at the heart of medicine development; this should be used as the foundation on which to build the PE framework in medicine development, unifying the interests of all healthcare stakeholders:

People succeed when they really internalise, recognise, and understand from their heart about the value of patients' voices. [P-06 (PX)]

Taking a human-centric design thinking approach in medicine development, you really adopt an attitude of empathy, to acknowledge that patients are the expert in their particular disease and patient experience counts to develop meaningful medicines for them. [P-02 (PX)]

I think patients can play an important role in medicine development which is driven by customer-focused thinking. ... PHARMA has understood that patients are the customers and the king. PHARMA would need to find a good business model and build up a platform and processes to enable patients to be engaged in these interactions. [P-08 (MD)]

I think patients are the consumers of the pharmaceutical products. That is why early involvement of patients to understand their needs is of paramount significance, which should be the primary driver for PHARMA to conduct research and design products to meet patients' need. [P-13 (MD)]

I think patients are our customers. We must focus on them to develop medicines which make sense for them. That is what I think the overall goal of PE in medicine development. [P-19 (MD)]

Drawing on the consensus from all healthcare stakeholders that patient value is the foundation for PE in medicine development, interviewees offered strong support for the

development of a multi-stakeholder-aligned PE methodology and process framework, and this was suggested to be a critical facilitator for advancing PE in medicine development currently. Narratives from interviewees present further insights and justifications:

> *I totally agree that we need to evaluate PE methodology, but you know there might be no one-size-fits-all method there. The question is how to apply the most suitable PE methodology to evaluate, such as functional loss versus cognitive loss versus emotional loss, etc. The methodology is under development and will move forwards, although it is still in the early days and might change significantly when it moves into the gene therapy era.* [P-17 (PT)]

> *Maybe we can learn the PE methods from the psycho-pharmaceuticals space where many social scientists working in this space, and we may use their knowledge to apply PE in the clinical trials. The other piece is to develop psychometric and social parameters to measure the quality-of-life impacts of medicine in addition to the biomedical parameters.* [P-29 (PT)]

> *You see that FDA has already issued guidelines regarding using PRO instruments in clinical trials and the usage of preference study, which may become a big deal on the road to influence regulatory decisions. FDA have already conducted three preference studies with patients' perspectives in their drug review, because they want to understand the maximum acceptable risks associated with a new drug from patients' perspective, instead of only from the opinion of PHARMA.* [P-30 (MD)]

> *I think it will be helpful if FDA can adopt some of the PE practices that PCORI uses – i.e., make determination about PE data requirements mandatory at each stage of the medicine development, particularly in the Phase 3 clinical trials – integrating psychometric measures with biomedical measures in the Phase 3 data collection.* [P-29 (PT)]

Taking the above discussions and narratives into consideration, it was evident that the *development of an aligned PE methodology and process framework*, endorsed by all relevant stakeholders (i.e., patients, PHARMA and regulators) was deemed to be a critical facilitator for the concept of PE in medicine development at the society level. This insight further substantiated the findings derived from the thematic analysis of the literature in the theoretical phase (see Section 4.3.1 and ***Table 7.1***).

(iii) 'PHARMA to integrate patients' voices in medicine development' – a facilitator for PE in medicine development at the PHARMA level

At the PHARMA level, interviewees suggested that the integration of patients' voices into the existing medicine development processes with right method is a key facilitator for PE to move forward at the PHARMA level (supported by 18 sources with 26 references from interviews). This was followed by other influencing factors, such as driving the necessary culture change (supported by 11 sources with 19 references from interviews) and developing measurement metrics to demonstrate PE outcomes (supported by 10 sources with 17 references from interviews). These identified key facilitators for the concept of PE in medicine development at the PHARMA level concurred with the findings derived from the thematic analysis of the literature in the theoretical phase (see Section 4.3.3 and ***Table 7.3***), yet offered more in-depth insight with a rich account of the rationales behind these identified

PE facilitators. Narratives from interviewees are offered below for further delineation and justification of these findings:

> *We need to understand patients' needs and the PE requirements of the competent authorities and try to bridge the methodology gap for meaningful PE in medicine development.* [P-19 (MD)]

> *PE will be a double win for both patients and PHARMA – in the end patients will get improved health outcomes, and PHARMA will get more benefits from the successful products. The only question is how to integrate patients' inputs with the scientific data along the medicine development processes. If patients' inputs can really inform a better product design – we do not see an example about how to do this yet.* [P-22 (MD)]

> *We need to educate both patients and researchers on how to do PE. We need to educate the patient community to create research-ready patient organisations who feel the power to communicate their voices; and we also need to train researchers on how to do PE in a meaningful way.* [P-02 (PX)]

> *I think there was little value in just listening to patients' stories without quantifying them in a meaningful way. ... Profound methodology to gather and analyse these patients' data is necessary to get the advantage of these patients' voices. So, I think the combination of active listening and providing a methodology to gather and analyse these patients' data will help the research.* [P-12 (PT)]

We need a specific group of people with the necessary knowledge and skills who know how to capture patients' inputs and incorporate these inputs to inform scientific research activities, which is currently a gap to be filled in the medicine development of PHARMA. [P-22 (MD)]

It seems to be a lot of talk about PE at the PHARMA company, … but the way that patients' inputs are gathered is very one-off approach, not systematic. From PHARMA company, PE needs to be designed, funded, mandated with a meaningful perspective. [P- 10 (PT)]

The insights gained from the above interviewees revealed that the good-will alone of PHARMA towards PE is not considered sufficient. PHARMA needs to design proper processes and methodology to integrate patients' voices in medicine development within PE in a meaningful way, and interviewees testified that this was a key facilitator for PE in medicine development at the PHARMA level.

Considering the above discussions overall, the *development of an aligned PE framework with multiple stakeholders along the medicine development life-cycle* was endorsed by interviewees as an overarching key facilitator of PE in medicine development (see ***Figure 9.5***). The implications of this finding are multiple. First, from a theoretical perspective, the aligned PE methodology and process developed needs to be embedded in a PE conceptual framework, which outlines the understandings of the concept of PE in medicine development (i.e., answering the *what* and *how* questions). This was, however, identified as a knowledge gap in both the current literature and the interviews (see Section 2.4; Section 4.3; Section 5.3.4). The RO3 of the present study (see Section 1.2) aims to develop a PE conceptual framework addressing *what* and *how* questions about PE in

medicine development, thus contributing to this knowledge gap (see Section 6.3). Secondly, from a practical perspective, the insights gained from interviewees offered further practical recommendations for healthcare stakeholders regarding how to facilitate PE in medicine development practices effectively (to be discussed further in Section 7.3). Knowledge of and action on identified facilitators for PE in medicine development can potentially contribute to effective implementation of PE in medicine development practice by actively addressing these facilitators and paving the way for a right implementation.

5.3 Summary

Drawing on in-depth analysis of interviews with relevant stakeholders, this chapter presented the findings from the fieldwork to address RO2 in the present study. It offered comprehensive empirical data regarding the perceptions and practical use of the concept of PE in medicine development from the multiple perspectives of key PE stakeholders (i.e., patients, medicine developers, and PE experts). As a result, a holistic understanding of PE in medicine development from multiple stakeholder standpoints was provided and RO2 was deemed to be addressed, offering a novel contribution to fill a critical knowledge gap in the current literature (Boutin et al., 2017; Domecq et al., 2014; Lowe et al., 2016).

Furthermore, this chapter offered a comprehensive account of the current use of the concept of PE in medicine development practices, including the contextual factors (i.e., antecedents, attributes, consequences, barriers and facilitators) which delineated the significance and contextual relevance of the concept of PE in medicine development from a value-creation perspective. These contextual factors were deemed necessary to offer a complete understanding of and give theoretical clarity to the concept of interest (Rodgers & Knafl, 2000), which had not been available from previous research (Frank et al., 2015; Hoos et al., 2015; Higgins et al., 2017). Therefore, the present study offers the first comprehensive understanding of this complex social phenomenon from a value-creation perspective, with

in-depth empirical evidence supporting a holistic account of the concept of PE in medicine development from a social constructivist stance. Interview findings endorsed further the multi-faceted characteristics and underlying contextual complexities of the concept of PE in medicine development beyond a simple concept analysis in this chapter.

In the next chapter, the findings from both the fieldwork and theoretical phases are triangulated and further discussed in relation to the theoretical perspectives (based on VBM, VCC and SDL) defined for the present study (see Section 2.5). Chapter 6 aims to offer greater theoretical clarity of the PE phenomenon by developing a conceptual framework for PE in medicine development, based on insights gained in the present study. This was suggested as a key facilitator (see Section 5.2.5 and ***Figure 9.5***) of critical, but currently missing knowledge to be addressed to advance PE in medicine development. Thus, Chapter 6 addresses this missing knowledge through RO3 in the present study.

6 Analysis and findings from the final analytical phase

6.1 Introduction

Following the research methodology framework designed for the present study (see ***Table 5***), the findings from the thematic analysis of the interviews and the literature are examined, integrated, discussed, and interpreted further in this chapter. The final analytical phase aims to offer a comprehensive account and congruent understanding of the concept of PE in medicine development from a value-creation perspective. The theoretical clarity of this concept is delineated and strengthened through the triangulation of different data sources from the literature and interviews and different perspectives of stakeholders. This chapter addresses RO3 of the present study by offering (a) a final definition of the concept of PE in medicine development, based on the identified key attributes of PE in medicine development at the level of the patient, society and PHARMA; (b) a comprehensive delineation of the contextual factors (antecedents, attributes, consequences and influencing factors) associated with the concept of PE in medicine development, within which the concept of PE in medicine development is used; and (c) the relationship of the concept of PE in medicine development with other identified related key concepts are delineated and discussed. In so doing, a conceptual framework for PE in medicine development is developed, connecting the concept of PE and other PE-related key concepts to offer a holistic account of the PE phenomenon in medicine development. Furthermore, the logical consistency of the PE conceptual framework developed with the value-creation theoretical perspective (based on VBM, VCC and SDL) is discussed.

As a result, a final thematic map of PE in medicine development, as developed from the final analytical phase, is provided in this chapter (see ***Table 10),*** which presents the final integrated themes (including indicators for each theme derived from the respective underlying thematic codes) regarding PE in medicine development based on interviews and

literature. A final PE definition in the context of medicine development is offered (see ***Table 15***). A conceptual framework for PE in medicine development is then developed, based on identified core themes and their relationships, as presented in Section 6.3 (see ***Figure 10***). Additionally, a detailed integrated thematic map, matching the themes, categories, and codes derived from the theoretical, fieldwork and final analytical phases, is provided (see ***Annex 10***). The aim is to support readers in retracing the process from codes to categories and themes as developed in the present study, thus providing transparency so readers may judge for themselves the data analysis processes performed in the final analysis phase.

6.2 Final triangulation and analysis of qualitative data

The concept development approach of Rodgers and Knafl (2000, p. 325) supports the idea that 'concepts are constructed and socially or contextually bound. This philosophical foundation supports the need to identify contextual variations, … to determine how the values and norms of that context have influenced the formation and use of the concept'. Following the philosophical foundation of Rodgers' (1989) concept development approach and the researcher's own social constructivist stance, a comprehensive exploration of PE in medicine development was undertaken based on the interviews and literature data, identifying antecedents, attributes, consequences and influencing factors in the present study. Thus, this study provides a holistic account of the PE phenomenon in medicine development, in line with the philosophical stance that 'a complete understanding of a concept, however, is possible only with a thorough exploration of its origin, contextual relevance, and implications, in other words, how and why the concept developed and the possible effects of the conceptualization on segments of society' (Rodgers & Knafl, 2000, p. 326).

People in different roles, with different perspectives (such as patients, medicine developers or PE experts) may have different understandings and thus attach different meanings to the concept of PE in medicine development, according to their respective

contextual variations. Therefore, an in-depth understanding of these diverse perspectives can offer valuable insight into how the concept of PE in medicine development is constructed by different stakeholders within their values and norms. In particular, understandings about how these perspectives are related to one another will enable a comprehensive and holistic account of a complex social phenomenon - such as PE in medicine development - to facilitate a consensus understanding.

Following this line of thought, triangulation of the data from different sources (i.e., interviews and literature) and different perspectives (i.e., patient, society, and PHARMA) was undertaken in the final analysis phase. As a result, a richer and fuller story about the concept of PE in medicine development was achieved, thus providing greater theoretical clarity to this complex social phenomenon, by filling an identified gap in the current body of knowledge (Boutin et al., 2017; Frank et al., 2015; Hoos et al., 2015). The final thematic map of PE in medicine development, developed from the final analysis phase by integrating and triangulating the themes identified from interviews (see Chapter 5 and ***Figure 9***) and literature (see Chapter 4 and ***Figure 8***), presents the consolidated contemporary understandings regarding the concept of PE in medicine development developed from the present study (presented in ***Table 10***), thus addressing the RO3 of the present study. These developed final themes of PE in medicine development are further elaborated upon in detail in the following sections.

Table 10: Final thematic map of PE in the context of medicine development

	Overarching Themes	PATIENT	SOCIETY	PHARMA
Antecedents (section 6.2.1)	Patient Centricity	**Patient as consumer & expert wants patients' voices to be heard (category)** Indicators (thematic codes): • Patient as consumer & expert • Patients' rights & ethics • Health literacy & capacity	**VBM requires presence of patients' voices in medicine development (category)** Indicators (thematic codes): • Driven by patient value • Innovation & sustainability • Paradigm shift to VBM	**PHARMA to adopt patient centricity - understand patients' needs & perspectives (category):** Indicators (thematic codes): • Patient-centric culture • PE guidance & incentives • Recognise the value of PE
Attributes (section 6.2.2)	Co-Creation	**Patient as value co-creator: Leverage patients' experience in living with disease as an asset (category)** Indicators (thematic codes): • The engaged patient • Patient as value co-creator • Presence of patients' voices	**Patients as partner in medicine review and approval processes of regulators (category)** Indicators (thematic codes): • Shared leadership • Patient as value co-creator • Partnership & collaboration	**Co-creation through combining knowledge and experiences of PHARMA and patients in interaction (category)** Indicators (thematic codes): • Integration of patient value • Patient as value co-creator • Partnership & collaboration
Consequences (section 6.2.3)	Improved Value	**Improved Patient Value (category)** Indicators (thematic codes): • Improved adherence & compliance • Improved relevance & adoption • Improved patient experience & trust	**Improved Healthcare Value (category)** Indicators (thematic codes): • Improved patient experience • Improved healthcare value • Improved healthcare sustainability	**Improved Business Value (category)** Indicators (thematic codes): • Improved patient value & healthcare value • Improved innovation & business success • Improved reputation & trust
Influencing factors (section 6.2.4)	PE Framework with aligned Value and Methodology	**Maturity of Patient Organisations – increased health literacy, capacity, and patient expert research network (category)**	**PE framework based on aligned value and methodology endorsed by multiple stakeholders (category)**	**Culture and process changes through integration of PE into medicine development lifecycle (category)**

6.2.1 *Antecedents* of the concept of PE in medicine development

The overarching theme regarding antecedents of PE in medicine development was identified by the final analysis in the present study to be *patient centricity*, which was indicated as being driven by: (i) increased importance of the patient as consumer and expert, at the patient level; (ii) the presence of patients' voices in medicine development in the shift to VBM paradigm, at the society level; and (iii) a patient-centric culture adopted at the PHARMA level. The integrated thematic map about the antecedents of PE in medicine development developed through corroborating data from the interviews and literature is presented in ***Table 11***.

Table 11: Integrated thematic map regarding antecedents of PE in medicine development

Overarching theme regarding ***antecedents*** of PE in the context of medicine development: ***Patient Centricity***			
Level	Final Analytical Phase (section 6.2.1)	Theoretical Phase (section 4.2)	Fieldwork Phase (section 5.2.1)
Society	***The presence of patients' voices in medicine development in the shift to VBM paradigm***	*Paradigm shift to VBM*	*Regulators & HTA ask for presence of patients' voices in medicine development required by VBM paradigm*
Patient	***Patient as Consumer & Expert***	*Patient as Consumer & Expert*	*Patient as Consumer & Expert wants patients' voices to be heard*
PHARMA	***Patient Centricity***	*Patient Centricity*	*PHARMA to adopt Patient Centricity to understand patients' needs and perspectives*

At the society level, VBM requires that the healthcare system be built on and measured around the health benefits achieved for patients, which should become the overarching goal of all healthcare stakeholders; therefore, value creation for patients should determine the rewards for all actors in the healthcare system (Brown et al., 2003; Porter, 2010). These VBM propositions, underlying the concept of PE in medicine development, were echoed by interviewees in the fieldwork: *the presence of patients' voices in the shift to VBM paradigm* was endorsed as a key antecedent of PE in medicine development at the society level (see Section 5.3.1). The paradigm shift to VBM has further challenged the prevailing paternalist attitude of HCPs who started to recognize the *patient as a consumer and expert*, and this was indicated as a key antecedent to PE in medicine development at the patient level (Baines & de Bere, 2018; Kirwan et al., 2017; Lowe et al., 2016).

At the patient level, recognizing the *patient as consumer and expert*, as an antecedent to PE in medicine development, was based on the wide consensus that patients are the beneficiaries of medical treatment and bear the potential risks; thus, patient value should be at the heart of any medical encounters, including medicine development (Hoos et al., 2015; Perfetto et al., 2015; Smith et al., 2016). This claim was endorsed by interviewees in the fieldwork (see Section 5.3.1).

At the PHARMA level, patients' experiential knowledge of living with a disease can add value to the knowledge of researchers; following this line of argument, medicine

development becomes patient-centred rather than only driven by science (Blasimme & Vayena, 2016). Therefore, PHARMA taking an authentic *patient centricity* attitude in medicine development within PE was suggested as a key antecedent to PE in medicine development at the PHARMA level (Carman et al., 2013; Kirwan et al., 2017), and was also supported by interviewees from the fieldwork (see Section 5.3.1).

Furthermore, interviewees argued that, given the broad acknowledgement of the patient as consumer and expert within a VBM paradigm, the case has been made for the moral imperative for PE in medicine development which affects on patients' lives. Following this agreed moral imperative for PE in medicine development, the requirements of regulators and HTA agencies to incorporate the patient voices in medicine development processes at the society level is likely to force PHARMA to adopt a patient-centric attitude. In this regard, PHARMA would have to adopt a PE approach in medicine development due to the extrinsic societal pressure from both patients and society (Blasimme & Vayena, 2016; Miseta, 2015a; Pushparajah, 2018; Yeoman, 2016). The relationships between these identified antecedents of PE in medicine development at the levels of patient, society, and PHARMA were strikingly illustrated by interviewees as follows:

> *PHARMA realised that PE is the right thing to do – to get the patients' voices involved, because patients' outcome is the value for healthcare; … and PHARMA would have to do the PE as well, because regulators started to mandate PE as minimum requirements. I think these two things joining together will end up in having patients become equal partners in the drug development process of PHARMA.* [P-06 (PX)]

> *I think a patient-centric medicine development is driven by the recognition by the* PHARMA *industry that the voices of people who are recipients of the medicine should be involved at various time points along the medicine development lifecycle. … And FDA asked for PE in the medicine development for the drug review approval and authorisation process. I think the regulators' requirements on PE have a large impact on the increased use of patients' perspectives in the medicine development of* PHARMA. [P-12 (PT)]

The above two interviewees referred to extrinsic factors (i.e., VBM at the society level, and patient as consumer and expert at the patient level), which are perceived to precede the adoption of patient-centricity by PHARMA within PE in medicine development. Nevertheless, interviewees also argued that an intrinsic motivation, based on a real appreciation of patient inputs within PE in medicine development, would be the desired, authentic, patient-centric culture that PHARMA should build-up, which was suggested as an important antecedent to the concept of PE in medicine development at the PHARMA level. An interviewee illustrated this aspect as follows:

> *What we want is the intrinsic motivation of the PHARMA researchers who believe that my work will become more open and interesting if I collaborate with the patients, and, at the end of the day, I will profit from the PE I am doing. And here the rewarding should also be intrinsic because PE is important to you. That is something which should be part of the culture and policy of the researcher's own PHARMA company.* [P-16 (PX)]

However, most interviewees considered that an authentic patient-centric culture at the PHARMA level had not yet been systematically demonstrated in current medicine development practices, which was frequently criticized as being an element missing from PE in medicine development both in the literature (see Section 4.3.3 and ***Table 7.3***) and the interviews (see Section 5.2.4 and ***Figure 9.4***). Furthermore, *patient centricity* – suggested as an overarching key antecedent of PE in medicine development by interviewees – underscored the congruence with the SDL perspective, which is inherently customer-centric and views the social and economic systems as collaborative environment for actors to co-create value based on integration of resources (Vargo & Lusch, 2004). Drawing on the principles of SDL that value is always determined by the beneficiary and the customer is always a co-creator of value, demanding an inherently customer-centric (i.e. patient-centric in medicine development) attitude (Prahalad & Ramaswamy, 2000; Vargo & Lusch, 2004) from all healthcare actors, PHARMA should not be the exception, if it wants to serve its customers well and thrive in competition (Carman & Workman, 2017; Collier, 2015; Crawford et al., 2017).

Taking the above discussions into consideration, *patient centricity* was proposed as the overarching antecedent of PE in medicine development in the present study, derived from the understandings of preceding events at the level of society, patients and PHAMA from the theoretical, fieldwork and final analytical phases in the present study (see ***Table 11***).

6.2.2 *Attributes* of the concept of PE in medicine development

The core defining attribute of the concept of PE in medicine development was suggested to be *co-creation* in the present study, as substantiated by both the literature analysis from the theoretical phase (see Section 4.2) and empirical interviews from the fieldwork phase (see Section 5.2.2). This core defining attribute of PE in medicine development was derived from three categories: (i) partnership and collaboration, at the

society level; (ii) patient as value co-creator, at the patient level; and (iii) integration of patient value in medicine development, at the PHARMA level (see ***Table 12***). An interpretation of these identified attributes of PE in medicine development, and their relationships to the value-creation theoretical perspectives (see Section 2.5), is offered in the following paragraphs for further conceptualization.

***Table 12**: Integrated thematic map regarding the attributes of PE in medicine development*

Overarching theme regarding ***attributes*** of PE in the context of medicine development: ***Co-Creation***			
Level	Final Analytical Phase (section 6.2.2)	Theoretical Phase (section 4.2)	Fieldwork Phase (section 5.2.2)
Society	***Partnership & Collaboration***	*Co-creation through Partnership & Collaboration*	*Patient as Partner: Integrate patients' voices in medicine review and approval processes of regulators*
Patient	***Patient as Value Co-Creator***	*Co-creation through Patient as value co-creator*	*Patient as Value Co-creator: Leverage patients' experience in living with disease as an asset*
PHARMA	***Integration of Patient Value***	*Co-creation through Integration of patient value*	*Integration of patients' voices in medicine development*

At the society level, the findings from the present study suggested that partnership and collaboration in clinical settings and policymaking was an established key attribute of PE in medicine development. This refers to having patients' voices heard, respected, and appreciated in all medical encounters, including medicine development activities (Batalden et al., 2016; Boutin et al., 2017; Tapp et al., 2017). Furthermore, this identified attribute of PE at the society level resonates with the VCC principle through a shared emphasis on co-creation in interactions between customers and firms (see Section 4.2 and Section 5.3.2). In this regard, PE was understood by the interviewees to be a process of interactions between medicine developers and the patient as value co-creator of positive health outcomes, to integrate patient value into medicine development processes through partnership and collaboration (see Section 5.2.2). These salient attributes of PE in medicine development, and their relevance to value-creation, were depicted vividly by interviewees as follows:

Everything we do in the PE space is multi-dimensional. … We define PE as a trustful relationship with mutual benefits. … It is built on PHARMA's appreciation that patients are ultimately consumers and research partners in medicine development. … PHARMA needs to demonstrate genuine interest in a long-term partnership for PE if they understood the value that patients can bring to the table. [P-02 (PX)]

For me, the value [of PE] ultimately means a positive outcome for the patient. If you are going to design the positive outcome for patient as value, you need to do it with the patient as a partner in this process. … The patients' perspective is now being recognised as an important part of that ecosystem. [P-06 (PX)]

I think partnership and collaboration are more beneficial than consultation in PE activities, because you can build up long-term relationships and allow each other to develop trust to become partners. … Scientists should gradually appreciate patients' experiences as a co-investigator in medicine development [P-11 (PX)].

Drawing on the above discussions, the present study proposed that *co-creation* of value for patients and all healthcare stakeholders within PE in medicine development is an overarching essential defining attribute of the concept of PE in medicine development (see ***Table 12***). Furthermore, *co-creation*, identified as a key attribute of PE in medicine development, shares a theoretical core with SDL, VCC and VBM perspectives: that value is determined by customers and customers who are always co-creators of value, which is also applicable in the context of PE in medicine development (Brown et al., 2003; Porter, 2010; Prahalad & Ramaswamy, 2004; Vargo & Lusch, 2004).

6.2.3 *Consequences* of the concept of PE in medicine development

The consequences of a concept answer question about what happens as a result of the concept (Walker & Avant, 2011). The overarching core consequence of the concept of PE in medicine development was suggested by the present study as *improved value* (see ***Table 13***), and this was supported by both the literature analysis (see Section 4.2) and the empirical interviews (see Section 5.2.3). Improved value for patients and all healthcare stakeholders, as an overarching core consequence of PE in medicine development, was supported by three categories in the present study: (i) improved patient value at the patient level; (ii) improved healthcare value at the society level; and (iii) improved business value at the PHARMA level (see ***Table 13***). These core themes concerning the consequences of PE in medicine development are further justified through the final integrated analysis of interviews and literature and, are interpreted from a value-creation perspective (see Section 2.5).

Table 13: Integrated thematic map regarding consequences of PE in medicine development

Overarching theme regarding *consequences* of PE in the context of medicine development: ***Improved Value***			
Level	Final Analytical Phase (section 6.2.3)	Theoretical Phase (section 4.2)	Fieldwork Phase (section 5.2.3)
Society	***Improved Healthcare Value***	*Improved Healthcare Value*	*Improved Healthcare Value*
Patient	***Improved Patient Value***	*Improved Patient Value*	*Improved Patient Value*
PHARMA	***Improved Business Value***	*Improved Business Value*	*Improved Business Value*

First, at the patient level, improved adherence and compliance, improved relevance and adoption of the developed medicines, and improved patient experience and trust were suggested to be the major positive factors contributing to the expected consequence of *improved patient value* associated with PE in medicine development (Ayton et al., 2018; Barello et al., 2015; Carroll et al., 2017). The interviewees further endorsed this predicted positive outcome which PE in medicine development can bring at the patient level. Most interviewees argued that PE in medicine development is the most effective way to develop

better medicines which will improve patients' health outcomes, thus leading to improved patient value. See below an illustration of this claim from one interviewee:

> *PE is about improving the patients' outcomes – that is the only goal here. I do not think there is disagreement that more robust, scientific patients' voices data will drive positive outcomes; that's why PE in medicine development needs to be encouraged.* [P-06 (PX)]

Secondly, at the society level, improved healthcare value – in terms of better treatment outcomes, quality, efficiency and sustainability, and improved patient experience (in terms of trust, respect, transparency, legitimacy, relevance, ethical fairness and accountability), were suggested from the analysis of the literature to be key consequences of the concept of PE in medicine development (Boutin et al., 2017; Carroll et al., 2017; Chiauzzi et al., 2016; Kendell et al., 2014; Kohler et al., 2017). Similarly, interviewees attested that the inclusion of PE throughout the medicine development lifecycle would allow the research agenda to be set considering both healthcare priorities (from a societal perspective) and the unmet medical needs of patients (from a patient perspective), so that the medicines developed by PHARMA would be more likely to improve the health outcomes of patients and healthcare value for society. Therefore, *improved healthcare value* was suggested as an expected beneficial consequence of PE in medicine development at the society level by interviewees (see Section 5.2.3). Some interviewees offered further insight about this anticipated consequence:

> *Keeping patients' voices and hopes involved through PE at very early stages of medicine development in considering what needs to be developed, and then decide*

on the research portfolio and pipeline would allow understandings about gaps for patients from public health perspectives to guide the medicine development agenda and maximise healthcare value. In my mind, this is the most impactful results that PE can bring value to the public health. [P-04 (PX)]

Greater PE will produce better research – more targeted research; it may not necessarily reduce costs, but it makes all the research more relevant to the patients, so it produces additional benefits for everyone. [P-07 (PT)]

Next, at the PHARMA level, improved patient value and improved healthcare value achieved by developing better medicines through PE were suggested in the literature to contribute to the business success of PHARMA in terms of greater innovation, increased financial benefits and improved reputation and trust (Bloom et al., 2018; Kirwan et al., 2017; Levitan et al., 2018; Sharma, 2015). Similarly, interviewees substantiated that the *improved business value* derived from PE in medicine development for PHARMA is in multiple ways:

(i) Operationally, PE in medicine development allows PHARMA to improve clinical trials, mitigate development risks through matching product profiles with patients' needs, show the presence of patients' voices in the data submission packages to health authorities, facilitate regulatory approval and achieve attractive product labels. All of these assumed positive consequences associated with PE in medicine development should contribute to the financial benefits of a PHARMA on an operational level. Some interviewees offered their perceptions to support this claim as follows:

The PE value for PHARMA is many things really: they get better studies, better understandings of what patients' needs are, … they may also get positive feelings

that patients are friends; at the moment, there is huge suspicion that PHARMA wants to screw people and is not interested in caring for patients. I think showing openness to criticism and ideas from patients through PE in medicine development can help PHARMA thrive commercially in the long run. [P-07 (PT)]

I think the PE benefit for PHARMA is to mitigate the risks of the medicinal products through matching the patients' preference with what the product can do for them within the scientific framework, to increase the probability that the products coming to the market are being successful – design a product appealing to patients with minimal cost. [P-05 (PX)]

(ii) Strategically, authentic PE activities throughout the medicine development process can build trust and goodwill between PHARMA and patients, allowing PHARMA to prove transparency, patient-centricity, and trustworthiness, which have been suggested to be important for PHARMA to thrive in the long-term by most interviewees. This strategic benefit of PE in medicine development for PHARMA was endorsed by interviewees as follows:

From a reputation perspective, the benefits for PHARMA are huge associated with PE in medicine development, to improve branding and trust, and to establish the image as a trustworthy company because we have engaged patients in a long way. The trust gained through joint medicine development is huge – those are intangible returns on investment associated with PE, although you may see the effectiveness of the PHARMA company evolve over time; … Again, PHARMA companies who do not see the benefits of PE will be very naive. [P-12 (PT)]

> *PHARMA has a bad reputation and are not very trusted by patients; PE can serve also a good-will trust-building between PHARMA and patients. PHARMA industries need to demonstrate themselves on global scale as honest, transparency, trustworthy partner through authentic PE in medicine development.* [P-02 (PX)]

Furthermore, the final integrated analysis of literature and empirical interviews suggested that improved patient value associated with PE in medicine development was perceived as the primary beneficial consequence expected at the patient level, followed by improved healthcare value at the society level and, subsequently, improved business value at the PHARMA level. These findings are in alignment with the VBM theory which emphasizes patient value as a foundational key concept unifying the expectations of healthcare stakeholders and sets out the rewards for the actors involved:

> Achieving high value for patients must become the overarching goal of health care delivery, with value defined as the health outcomes achieved per dollar spent. This goal is what matters for patients and unites the interest of all actors in the system; … value should be always defined around customers, … the creation of value for patients should determine the rewards for all actors in the system. (Porter, 2010, p. 2477).

However, despite the predicted positive consequences of PE in medicine development, limited empirical evidence can be found in the literature to validate this association. The lack of empirical test data in the literature could be partially explained by the fact that there is still no shared understanding of PE in medicine development. If the core components of a concept (i.e., what PE in medicine development means) are not yet

defined, it is not possible to measure its consequences. Furthermore, an aligned methodology framework of how to carry out PE in medicine development is still lacking, with no guide to meaningful PE in practice. Consequently, the predicted consequences of PE in medicine development cannot be accurately measured in practice if the questions of '*what* and *how*' about PE in medicine development remain to be answered. This further underscore the significance of the contribution from the present study, which aims to answer these questions of '*what* and *how*' of PE in medicine development, filling this gap in knowledge by offering a foundational basis for future testing and measurement.

As illustrated in ***Table 10***, the final thematic map developed from the present study offers a comprehensive answer to what PE in medicine development mean at the level of society, patient, and PHARMA. This allows future hierarchical testing of the identified attributes and associated indicators at the level of society, patients, and PHARMA respectively, to demonstrate the presence of the concept of PE in medicine development as a social phenomenon. For instance, the *co-creation* core attribute of PE in medicine development can be measured by the attributes at the level of patient, society, and PHARMA respectively, to show the complete presence of this concept (see ***Table 10***):

(a) '*patient as value co-creator – leverage patients' experience in living with disease as an asset*' at the patient level (which can be further measured by the indicators of (i) *the engaged patient*; (ii) *patient as value co-creator*; and (iii) *presence of patients' voices*);

(b) '*patients as partner in medicine review and approval processes of regulators*' at the society level (which can be further measured by the indicators of (i) *shared leadership*; (ii) *patient as value co-creator*; and (iii) *partnership and collaboration*); and

(c) '*co-creation through combining knowledge and experiences of PHARMA and patients in interaction*' at the PHARMA level (which can be further measured by the indicators of (i) *integration of patient value*; (ii) *patient as value co-creator*; and (iii) *partnership and collaboration*).

All these attributes and indicators should be tested to demonstrate the presence of a meaningful PE in medicine development. Analogue to the testing of attributes of PE in medicine development, identified themes and indicators for antecedents and consequences of PE in medicine development at the level of patient, society, and PHARMA can be also tested to demonstrate the presence of antecedents and the anticipated consequences of PE in medicine development respectively (see ***Table 10***).

The next section elaborates upon further the factors influencing PE in medicine development, derived from the barriers and facilitators identified from the literature and interviews. These offer further contextual understandings and practical use of the concept of PE in the context of medicine development.

6.2.4 *Influencing factors* of the concept of PE in medicine development

Rodgers' (1989) evolutionary concept development approach emphasizes the identification of the contextual basis in the sociocultural application of the concept, which was considered useful for understanding the status, significance, and effectiveness of the use of a concept under contextual constraints. Influencing factors consider the barriers to and facilitators for a concept by delineating the issues that need to be addressed, and how these issues can be tackled appropriately for the effective use of a concept in practice (Rodgers & Knafl, 2000).

Following Rodgers' (1989) line of thinking, factors influencing PE in medicine development were investigated in the present study. As a result, the *development of a PE*

framework with aligned value and methodology throughout the medicine development lifecycle was identified as an overarching major influencing factor for the concept of PE in medicine development. This finding was supported by both the literature analysis (see Section 4.3) and the empirical data from the interviews (see Section 5.2.5). This overarching major influencing factor to PE in medicine development was derived from analysis of influencing factors at different levels of stakeholders: (i) a PE framework based on aligned value and methodology endorsed by multiple stakeholders at the society level; (ii) the maturity of POs with increased health literacy, capacity, and patient expert research network at the patient level; and (iii) culture and process changes through integration of PE into medicine development lifecycle at the PHARMA level (see ***Table 10***). These influencing factors illustrated by respective stakeholders, however, pointed to the same need to develop an aligned *PE framework with aligned value and methodology*, urgently needed to guide the joint PE activities of the stakeholders in the context of medicine development (see ***Table 14***).

Table 14: *Integrated thematic map regarding factors influencing PE in medicine development.*

Overarching theme regarding ***influencing factors*** of PE in the context of medicine development: ***PE Framework with aligned Value and Methodology***			
Level	Final Analytical Phase (Section 6.2.4)	Theoretical Phase (Section 4.3)	Fieldwork Phase (Section 5.3.5)
Society	***PE framework based on aligned value and methodology endorsed by multiple stakeholders***	*Development of a PE conceptual framework with aligned value endorsed by all healthcare stakeholders*	*Develop multi-stakeholder-aligned PE methodology and process framework*
Patient	***Maturity of Patient Organisations – increased health literacy, capacity, and patient expert research network***	*Development of aligned methodology to incorporate meaningful patient input*	*Engagement of the right patients with the right purpose*
PHARMA	***Culture and process changes through integration of PE into medicine development lifecycle***	*Development of aligned PE process framework endorsed by all healthcare stakeholders*	*PHARMA to integrate patients' voices in medicine development*

Additionally, these identified influencing factors of PE in medicine development further substantiated the notion that PE in medicine development is a complex social phenomenon, which can be advanced only if all the influencing factors at different levels are addressed in an integrated manner (Bae, 2015). It is not possible to address these issues in

the absence of a master *PE framework with aligned value and methodology*, endorsed by all healthcare stakeholders. Addressing this knowledge gap and critical influencing factor was, therefore, suggested as pivotal for future research into the concept of PE in medicine development. The meanings and significance given to this critical influencing factor of PE in medicine development were underlined by interviewees as follows:

> *We need to come to the point to have a common alignment on the value proposition among stakeholders to constitute some marriage of the value perspectives of medicine developers, regulators, payers, and patients; … at least aligned towards the clinical outcomes everybody can agree upon. In the end, the value is defined by the clinical outcomes of patients – this is a universal construct. But how to get there and how the value for patients can be created depends on the developers, regulators, and payers; and is influenced by these actors along the value-chain of the medicine development lifecycle. … I think the challenge is really the lack of a solid* PE *framework.* [P-12 (PT)]

> *There is a huge misalignment about data requirements, considering that it is very expensive and time-consuming to measure different parameters in medicine development. One opportunity in this regard is the core-outcome-set development for certain diseases, where all the stakeholders can put their stamps on, which must be measured in the clinical trials.* [P-26 (PT)]

Developing a comprehensive PE master framework in the context of medicine development to address all the issues and barriers as discussed above would demand enormous time and effort, and the involvement of all relevant healthcare stakeholders, but was clearly identified as a major knowledge gap and pivotal facilitator of PE in medicine

development (see ***Table 14***). As a starting point, a conceptual framework for PE in medicine development (RO3) developed in the present study (see the following Section 6.3) lays the foundations for the further development of a detailed master PE methodology and processes framework based on consensus understanding and aligned values, which was suggested to be urgently needed by all healthcare stakeholders (see Section 4.3; Section 5.2.5).

6.3 The development of a PE conceptual framework in medicine development

The purpose of this section is to develop a conceptual framework for PE in medicine development from a value-creation perspective. The PE conceptual framework was developed based on the triangulation of the findings as discussed above in Chapters 4–6. A conceptual framework is a tentative theory interpreting the phenomenon, which offers links between the concepts and supports further development of the theory, since concepts are the building blocks of theory (Maxwell, 2012). Within a conceptual framework with clearly defined indicators, the concept becomes measurable, and measurement is an essential next step for the further operationalization and advancement of concept development in social science (Bryman, 2015; Rodgers, 1989). Furthermore, a conceptual framework, as a theoretical abstraction of a phenomenon, can help us to understand the real world through showing the relationships between themes and their impacts on the phenomenon (Creswell, 2017). Thus, a conceptual framework is a useful tool in showing coherence in research, through establishing the links between empirical data and theory (Braun & Clarke, 2013; Bryman, 2015).

Following the above line of thought, a thematic analysis of all qualitative data was used in the present study as a systematic interpretive process to generate themes and identify patterns within the data, in order to offer a rich and insightful understanding of a complex phenomenon – PE in medicine development – and expand on existing theory. Furthermore, a conceptual framework moves the research beyond the descriptive into the realm of the

explanatory, through interweaving isolated empirical findings into a coherent piece for wider application (Ngulube, Mathipa & Gumbo, 2015). Other than theory generalization, themes may also be developed into a conceptual framework, showing patterns and interconnections in these themes inductively, guided by theoretical perspectives, in the form of pattern theories, described as the endpoint of qualitative research by Lincoln and Guba (1985). Developing a conceptual framework lies beyond Rodgers' (1989) evolutionary approach for concept development, which was however considered valuable in addressing an identified gap in knowledge (see ***Table 2***) by offering greater theoretical clarity to the concept of PE in medicine development, thus addressing RO3 of the present study (see Section 1.2).

To address the RO3 of the present study, qualitative data from the literature and interviews were synthesized in the final analysis phase by examining, integrating and refining the initial categories and themes until the whole picture emerged, whilst remaining grounded in the data collected from the present study through constantly referring back to the transcripts and codes, and checking meanings and patterns across the datasets (J. Smith & Firth, 2011). In doing so, a conceptual framework for PE in medicine development was developed in the present study (see ***Figure 10***). The conceptual framework aims to offer a holistic account and interpretation of the concept of PE in medicine development through a visual diagram delineating the relationships of the identified core themes, grounded in the final thematic map developed from the present study (see ***Table 10***) and further interpreted from a value-creation theoretical perspective. Further discussion and justification of this conceptual framework for PE in medicine development are provided in this section, with a focus on illustrating the relationships among the identified core themes within the PE framework and their links to the theoretical perspectives based on SDL, VCC and VBM, thus offering advanced theoretical clarity by demonstrating coherence and consistency.

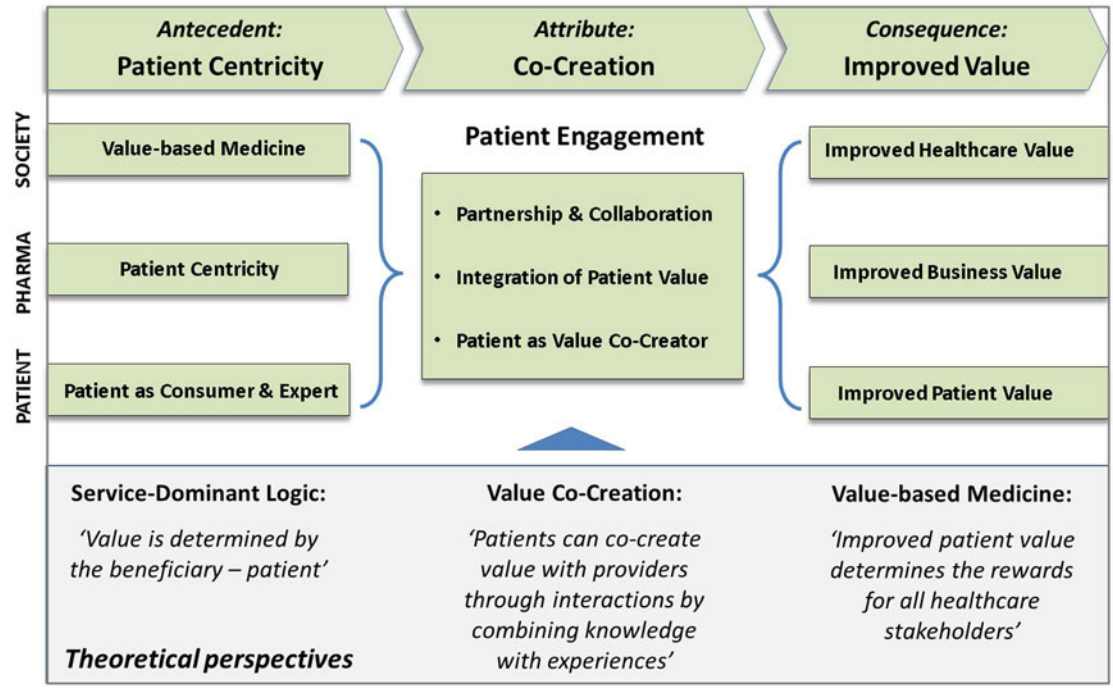

***Figure 10**: PE conceptual framework in medicine development developed from the final analytical phase*

Firstly, as discussed in Section 6.2.2, the overarching defining attribute of the concept of PE in medicine development was identified in the present study as *co-creation*, which includes the core components of:

- partnership and collaboration, at the society level;
- the patient as value co-creator, at the patient level; and
- the integration of patient value, at the PHARMA level.

Co-creation – the overarching, defining attribute of the concept of PE in medicine development – shares a theoretical core with VCC theory, because VCC postulates that customers have an active role to play in co-creating value together with the company through interactions, thus linking the market offerings of providers (ViE) with the customer's fulfilment of value (ViU) (Prahalad & Ramaswamy, 2000). Next, the identified key attribute of PE in medicine development at the patient level – *the patient as value co-creator* – aligns with the key proposition of SDL theory that the customer is always a co-creator of value (Vargo & Lusch, 2008). Further, the identified key attribute of PE in medicine development

at the PHARMA level – the *integration of patient value* in medicine development – resonates with VBM theory which emphasizes incorporating patient value into medical practices (M. M. Brown and Brown, 2013). Therefore, the demonstrated congruence of the defining attributes of PE in medicine development with the theoretical perspectives (based on SDL, VCC and VBM) substantiated the findings in the present study, while also underpinning the suitability of the defined theoretical perspectives for addressing the research questions.

Secondly, as discussed in Section 6.2.1, the overarching core antecedent of the concept of PE in the context of medicine development was identified in the present study to be *patient centricity*, which covers the core components of:

- value-based medicine (VBM), at the society level;
- the patient as consumer and expert, at the patient level; and
- patient centricity at the PHARMA level.

Both the literature (Brown et al., 2013; Lowe et al., 2016) and the interviews (see Section 5.2.1) suggested that VBM at the society level, and the patient as consumer and expert at the patient level, were preceding occurrences to patient centricity at the PHARMA level (see Section 6.2.1), which are all necessary antecedents for PE in medicine development to take a shape as a social phenomenon. This pattern could be partially interpreted to mean that PHARMA must adopt a patient-centric attitude in medicine development due to the extrinsic pressures coming from society and the patient (Marzorati et al., 2017; Smith et al., 2016). On the other hand, an authentic patient-centric culture in PHARMA, arising from a position of intrinsic appreciation of patient value in medicine development, is considered an important antecedent to PHARMA adopting true PE in medicine development with impact.

Thirdly, as discussed in Section 6.2.3, the *improved value* for patients and all healthcare stakeholders was suggested as the overarching core consequence of the concept of PE in medicine development in the present study, and includes the key components of:

- improved patient value, at the patient level;
- improved healthcare value, at the society level; and
- improved business value, at the PHARMA level.

Next, the final integrated analysis of the literature and interviews suggested that *improved patient value* at the patient level was perceived as the immediate primary positive consequence that PE in medicine development will entail, followed by *improved healthcare value* at the society level as a collective consequence. Finally, *improved business value* at the PHARMA level was considered as a natural consequence if PHARMA could demonstrate value for patients and healthcare within PE in medicine development (see Section 6.2.3). Furthermore, these proposed consequences of PE in medicine development from the present study resonate with the theoretical claim from a VBM perspective: improved patient value determines the rewards for all healthcare stakeholders (G. C. Brown et al., 2003; Porter, 2010).

However, despite the substantial arguments and considerable number of data sources supporting expected positive outcomes for PE in medicine development at different levels, little empirical measurement data could be found to validate these claims. The reasons for this existing knowledge deficit could be multiple, and needs to be tackled from different angles:

(i) Before PE outcomes can be empirically measured, a set of measurement metrics based on a common understanding of the key components of PE in medicine development is needed but this is, however, still lacking (Domecq et al., 2014; Perfetto et al., 2015);

(ii) PE, as an emerging concept in medicine development, could potentially transform existing medicine development paths to deliver the predicted positive outcomes, but could also add complexity to existing medicine development processes (Frank et al., 2015). It is not, therefore, surprising that the notion of PE in medicine development has encountered cultural resistance, and it will take time to deliver measurable positive outcomes (Boutin et al., 2017; Lowe et al., 2016); and

(iii) Generating empirical evidence, through measuring the outcomes of real PE initiatives in medicine development, could require considerable investment in terms of both cost and time on the part of all healthcare stakeholders so that funding and responsibility will be the subject of much debate (Boudes et al., 2018).

Drawing on the above arguments, the conceptual framework for PE in medicine development developed in the present study (***Figure 10***) addressed this knowledge deficit by offering a first reference model for PE in medicine development. It was developed from a social constructivist stance through delineating PE in medicine development as a complex social phenomenon which requires multiple factors to be addressed at different levels by the respective stakeholders. This holistic picture of PE in medicine development overcame the limitations of the narrow views of PE in medicine development in the current literature (Higgins et al., 2017; Hoos et al., 2015), thus providing a more profound foundation for the future measurement of PE in medicine development. For instance, identified categories and indicators associated with each core themes of PE in medicine development at all three levels (patients, society, and PHARMA) (see ***Table 10***) offer measurement metrics to test the presence of antecedents, attributes, and consequences of PE in medicine development at different levels, and to further develop this concept through practical application and

demonstrating significance in real-life use, which is in line with Rodgers' (1989) evolutionary concept development approach.

Additionally, drawing on the findings about key attributes of PE in medicine development at the level of the patient, society and PHARMA from the final analysis phase (see Section 6.2.2), a final definition of PE in the context of medicine development was proposed by the present study (see ***Table 15***).

Table 15: Final definition of the concept of PE in medicine development from the present study.

Patient engagement in medicine development means ***co-creation of value*** for patients, healthcare and all healthcare stakeholders through ***partnership and collaboration*** between healthcare actors and patients along the medicine development lifecycle, to allow ***integration of patient value*** in medicine development by engaging the ***patients as value co-creators*** *of health outcomes.*

The originality of this proposed final definition of PE in medicine development lies in its view of the concept of PE as a multi-dimensional social phenomenon, situated within a complex ecosystem involving multiple healthcare stakeholders with diverse perspectives in terms of values and expectations. Thus, there is no single true PE reality in medicine development waiting to be discovered and confirmed in the real world, as believed by scholars adopting a realist ontological stance. Rather, the meanings of PE in medicine development are deemed to be socially constructed (Creswell, 2017; Burr, 2003) by healthcare stakeholders through social interactions to co-create value for patients and all healthcare stakeholders. A qualitative inquiry, with a conscious interpretation of the constructed meanings offered by the relevant stakeholders (i.e., patients, medicine developers, PE experts) in the present study, allowed a holistic account of this PE phenomenon, reflecting the meanings for the relevant key stakeholders within a consensus PE definition in medicine development (see ***Table 15***). Thus, this final definition of PE in

medicine development, developed in the present study, offers a piece of original work, and expands the current knowledge base.

Furthermore, the value-creation theoretical perspectives adopted in the present study, based on SDL, VCC and VBM (see Section 2.5), proved useful in aiding the researcher to make sense of the data and interpret the findings. Most of the current literature investigates the PE phenomenon from the ethical and social justice standpoints; no earlier publications were found which explored the concept of PE in medicine development from a SDL, VCC or VBM theoretical perspective, which the present study does. Consequently, the present study offers a fresh theoretical perspective, generating new insights about the PE phenomenon from a value-creation perspective; and the conceptual framework developed for PE provides a comprehensive understanding of PE in medicine development, based on novel insights gained from relevant stakeholders and synthesized with the current knowledge base, thus creating an aligned understanding of this concept among users.

6.4 Theoretical propositions of PE in medicine development from a VCC perspective

Theoretical propositions are a set of coherent statements that purport to explain a given social phenomenon, which are used to explain the relationships among related concepts (Walker & Avant, 2011). Developing theoretical propositions based on observed relationships of related concepts are a major step towards theory construction, because theory requires that relationships among concepts are understood and predictable (Bryman, 2016). Following this line of thought, theoretical propositions of PE in medicine development were further developed from a VCC perspective to advance the theoretical development of this concept and address the RQ3 in the present study.

Drawing on the insights that co-creation is the underlying core attribute, improved value as core consequence for PE in medicine development (see ***Figure 10***), RQ3 was further elaborated upon considering the VCC perspective, which is primarily concerned with three

key questions: (i) what kind of value for whom (Value); (ii) by what kind of resources (Co-); and (iii) through what kind of mechanism (Creation) (Saarijarvi et al., 2013) (see Section 2.5.2 and ***Figure 3***). In so doing, a set of theoretical propositions about PE in medicine development was derived to answer these questions related to the RQ3 (presented in ***Table 16***). These theoretical propositions were developed through in-depth interrogation of the identified core themes and their relationships concerning PE in medicine development and interpreted from a VCC theoretical perspective. Further justifications of these theoretical propositions supported by narratives of interviewees are offered in the next paragraphs.

Table 16: Theoretical propositions of PE in medicine development from a VCC perspective

VCC aspects	**Theoretical propositions regarding PE in medicine development developed from a VCC perspective**
[Value] *What kind of value for whom?*	i. PE contends that integration of patient value in the medicine development lifecycle will allow the development of better medicines for patients, and generate ***value for patients, healthcare, and all healthcare stakeholders.***
[Co-] *What kind of resources?*	ii. PE acknowledges that patients are consumers of medicines and experts in living with diseases; their ***perspectives and experiences are valuable assets*** to be integrated in the medicine development lifecycle to complement ***scientific knowledge*** of HCPs.
[Creation] *What kind of mechanism?*	iii. PE allows scientific knowledge of HCPs to be combined with patients' experiences through ***interactions in co-prioritization, co-planning, co-implementation, co-dissemination, and co-measurement along the medicine development lifecycle.***

<u>Proposition (i):</u> PE contends that integration of patient value in the medicine development lifecycle will allow the development of better medicines for patients, and generate value for patients, healthcare, and all healthcare stakeholders.

This theoretical proposition draws on the relationships of the identified core attribute of PE in medicine development at the PHARMA level (i.e., integration of patient value) and the consequences of PE in medicine development (i.e., generating value for patients, healthcare and all healthcare stakeholders) (see ***Figure 10***). It answers the question about what kind of value for whom (*'Value'*) regarding PE in medicine development with emphasis on patient value as the overarching goal of all healthcare stakeholders within PE in medicine development, which will lead to value-creation for patients, healthcare, and all healthcare

stakeholders consequently. Further, this proposition resonates with the theoretical core of VCC, SDL and VBM, stating that value is determined by the patient (i.e., the customer) – the beneficiary of medicine development (Brown et al., 2010; Prahalad & Ramaswamy, 2004; Vargo & Lusch, 2004), and the improved patient value should determine the rewards for all healthcare actors (Porter, 2010) – i.e., improved healthcare value for society and improved business value for PHARMA. Consequently, *improved value for patients, healthcare, and all healthcare stakeholders* provides an answer to the question of *what kind of value for whom* ('*Value*') regarding PE in medicine development. Three interviewees underscored this theoretical proposition from their experience in the roles of patient, PE expert, and medicine developer respectively:

> *The medicine development needs to test the patients' acceptance and put them into their daily routine. It also depends on the payer who makes the determination that if this is something that could generate value for patients. There are several pathways to find out the acceptance of the medicines by patients if they like to take it, and if the payers are ready to pay for it based on the clinical outcomes of the patients. I think taking all these aspects together, the medicine developers need to think about what kind of clinical outcomes are relevant for patients and can these outcomes be anticipated with the developed drug; and the payers are willing to pay for it already in the medicine development processes. Payers will reimburse the medicine based on the value – so this is the value creation there. … We need to come to the point to have a common alignment on value proposition among stakeholders – to constitute some marriage of the value perspectives of developers, regulators, payers, and patients. Not necessarily always the same, but at least aligned towards the clinical outcomes everybody can agree upon. In the end the value is defined by the clinical outcome of patients – this is a universal construct.* [P-12 (PT)]

I think Patient's Voice is an extremely powerful tool in the HTA decision. HTA is increasingly using the Quality measures to judge the value of the treatment. We are all moving towards the value-based reimbursement system. The question is that how you define what VALUE means. For me, the VALUE ultimately means the Positive outcome for patient. If you going to design the Positive Outcome for patient as VALUE, you need to do it with Patient Voices as part of the processes. [P-18 (PX]

If a company develops a medicine for the patient who must take that and pay for it, we need to make sure that medicine will meet patients' need. If the medicine does not meet the patients' need, it will be harder and harder for the healthcare system to pay for it. … Having that said, the only way to understand patients' need is to talk to the patients. So, it is about to get patients' inputs on the problems that they want to be solved, and then put all research resources and effort to solve that problems. Secondly, it is about to get patients' inputs on how we should be doing it. … So fundamentally, we are shifting from thinking that doctors are the customers to considering patients as the consumers, so the medicines developed should meet the patients' needs rather than the doctors' needs. [P-27 (MD)]

Here, the above three interviewees have elucidated the importance of integrating the patient's perspectives into the medicine development of PHARMA through PE to create a holistic view of the medical outcomes. In doing so, the perspectives of the patient's quality of life will be considered in the clinical study design, so that patients, society, and PHARMA will all eventually benefit from better-developed medicine that can help the patients by demonstrating improved patient value. Thus, the above interview narratives provide an insightful practical illustration to support theoretical proposition (i) (see ***Table 16***).

<u>Proposition (ii)</u>: PE acknowledges that patients are consumers of medicines and experts in living with diseases; their perspectives and experiences are valuable assets to be integrated in the medicine development lifecycle to complement the scientific knowledge of HCPs.

This theoretical proposition draws on the relationship between the identified core antecedent of PE at the patient level (i.e., the patient as consumer and expert) and the core attribute of PE at the PHARMA level (i.e., the integration of patient value) in the context of medicine development (see ***Figure 10***) to answer the '*Co-*' question from a VCC perspective. The proposition postulates that patients' perspectives and experience are resources that should be brought in to complement the scientific knowledge of HCPs within PE in medicine development, thus addressing the question of *what kind of resources* ('*Co-*') are needed in PE in medicine development. Furthermore, this PE proposition in medicine development aligns with the SDL theoretical perspective that the customer is always a co-creator of value (Vargo & Lusch, 2004) and the emphasis on incorporating patient value in medical interactions from a VBM theoretical perspective (Brown et al., 2003; Porter, 2010). Therefore, patients' perspectives and experiences are an asset within PE in medicine development, offering a justified answer to the ('*Co-*') question (i.e., what kind of resources) regarding PE in medicine development. Interviewees from the group of patients, PE expert, and medicine developer offered further argumentations to endorse this proposition from their personal experience:

> *PE means for me that the patient knows about their illness. Lots of patients have to manage their daily life and they invent things. ... PHARMA should capture this knowledge from patients. ...I have used three injectable medicines from different companies for my disease and they are all ridiculous in a sense: e.g., it cannot help me to inject myself with one hand and I don't know how to cool them when I am on*

trip; these wishes seem to be so obvious for patients when they have to apply it every day… But if PHARMA did not talk with patients, how can they offer products that reflect patients' needs. These are small things, but I am convinced that patient experiences have a big impact on the compliance and the efficacy of the medicine. …Only patients have the knowledge about living with that disease in daily life. The usability and experiences shared by patients are the intangible aspects regarding a medicine that PHARMA should know to develop better medicines that patients want to take. [P-03 (PT)]

PE ensures that PHARMA can reflect the needs of patients in their medicine development; additionally, PE can improve trust, reputation, transparency of PHARMA, and bring lay users and scientists closer to each other, because patients normally know what works and what does not. You see, opening dialogue at different levels and exchange perspectives are important rather than just treating patients as subjects. [P-32(PX)]

You asked for drivers for PE in medicine development – there are several. The measurement of medical treatment effect is moving from population to individual; you see this manifested everywhere, you see that mass production is giving way to customization to individual's needs more and more. As part of this trend the societal expectation is that individual's needs are gaining importance in comparation to what the whole population – this is happening on the societal level. On the patient level, they are willing to take care of their own care, which probably started at the point of care, in terms of patients want to decide with the physicians how they want to be treated where patients have the most say. Patient Advocacy group (PO) has

translated it as – well, we should push to have these properties relevant to patients in the drugs being developed, we should push PHARMA to use the endpoints in clinical trials which are most important to patients. … These are important examples demonstrating that PE can make a difference and patients can make an influence on regulatory policy and PHAARMA company's decision making – so it is like a snowball. [P-30 (MD)]

From the perspectives of patient, PE expert, and medicine developer respectively, the above three interviewees vividly illustrated that valuable patient knowledge and experience of living with a disease can complement the scientific knowledge of HCPs (including PHARMA) through PE in medicine development to develop better medicines. Patients' perspectives and experiences are intangible assets which PHARMA should capture within PE in medicine development, to develop better medicines that meet the needs of patients – the consumers of medicines. The narratives of the above interviewees thus offer further practical meanings to endorse the PE theoretical proposition (ii) (see ***Table 16***).

Proposition (iii): PE allows scientific knowledge of HCPs to be combined with patients' experiences through interactions in co-prioritisation, co-planning, co-implementation, co-dissemination, and co-measurement along the medicine development lifecycle.

This theoretical proposition addresses the question of what kind of mechanism ('*Creation*') within PE in medicine development from a VCC perspective. The answer was suggested to be found through *interactions in co-prioritization, co-planning, co-implementation, co-dissemination, and co-measurement along the medicine development lifecycle* (see Section 6.2.2). These activities cover the complete medicine development lifecycle, where patients and PHARMA can co-create value to develop better medicines within PE. The proposition claims further that HCP's scientific *knowledge* and patients' *experiences* should be recognized as resources and integrated through *interactions* within

PE in medicine development, which serve as mechanisms to deliver improved patient value, healthcare value, and business value (see discussion in Section 6.2.2 and ***Figure 10***). These mechanisms, therefore, address how PE in medicine development can be applied in a meaningful manner. Furthermore, this PE theoretical proposition aligns with the theoretical core of VCC: that customers can co-create value with the firm through linking customers' *experience* with the *knowledge* of the firm through *interaction* (Prahalad & Ramaswamy, 2004) (see Section 2.5 and ***Figure 3***). Interviewees offered further insights, supporting this theoretical proposition of PE in medicine development from their perspectives:

> *I think that co-creation is exactly the format and mandate for PE in the medicine development, otherwise we will not get there. That is why involving professional PO in the drug development is so essential. I think many PHARMA are working on co-creation through capturing inputs from focus groups or involving them in their data monitoring board and steering committee, and integration of patients across their whole drug development paradigm.* [P-17 (PT)]

> *I think PE means that patients' perspectives and experiences brought to the table are recognised as being as valuable as the scientific knowledge of physicians and the other professions in the PHARMA company. ...PHARMA should set up a structure, such as a Patient Advisory Board, to engage patients early on and periodically throughout the drug development in different interactions. It is not a one-shot effort, but throughout the whole development process at different points.* [P-04 (PX)]

> *PE in the medicine development is needed from the very beginning to the end through the entire chain, only the extend of PE differ at different stages and moment.… Patient organisations are really becoming an official partner in the three-party meetings [Regulator, Patients, PHARMA].… PE needs to be put into the medicine development methodology processes. Along the medicine development processes we should have regular checkpoints regarding the PE.* [P-20 (MD)]

To summarize, three theoretical propositions of PE in medicine development (as discussed above) were developed from the themes and their relationships as illustrated in the PE conceptual framework in the present study (see ***Figure 10***). These theoretical propositions demonstrated further logical congruence with the value-creation theoretical perspectives based on VBM, VCC and SDL. As a result, these theoretical propositions about PE in medicine development provide justified answers to RQ3 in the present study, through addressing questions of how value can be co-created within PE in medicine development from a VCC perspective. The theoretical propositions regarding PE in medicine development offer advanced theoretical understanding about the PE phenomenon in medicine development, which therefore fills a critical knowledge gap in the present literature.

Taking the above discussions into overall consideration, the PE theoretical propositions and conceptual framework in medicine development are presented in ***Figure 11***. These findings offer an advanced theoretical clarity about PE in medicine development, thus filling a crucial knowledge gap in the extant literature (see ***Table 2***). Nevertheless, these theoretical propositions of PE in medicine development, as developed from a VCC perspective in the present study, are heuristic and exploratory, although they do offer a first interpretation of the PE phenomenon with hypotheses for future testing to advance theory development regarding PE in medicine development.

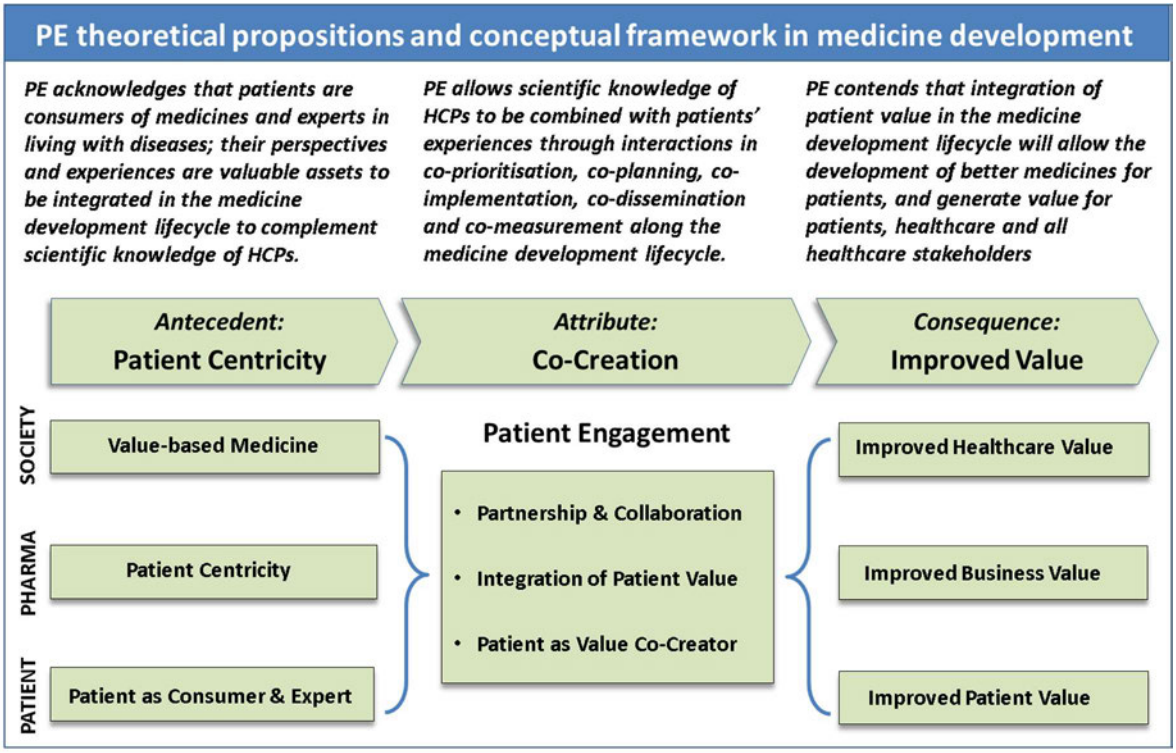

***Figure 11**: PE conceptual framework with theoretical propositions in medicine development*

6.5 Summary

This chapter presented the synthesized results through a final integrated analysis of all qualitative data gathered from both the literature and the interviews in the present study. Firstly, a final thematic map of the concept of PE in medicine development was presented, covering the antecedents, attributes, consequences, and influencing factors of this concept at the level of the patient, society, and PHARMA respectively (see ***Table 10***).

First, the findings suggested that *patient centricity* is the primary antecedent to the concept of PE in medicine development, which was driven by the paradigm shift to VBM, with patients increasingly acknowledged as consumers and experts by all healthcare stakeholders, and the increased patient centricity attitude taken by PHARMA.

Next, *co-creation* was proposed to be the overarching core attribute of PE in medicine development, referring to the collaboration and partnership between healthcare stakeholders to ensure the integration of patient value by recognizing the patient as a co-creator of value. These attributes must be present within an authentic PE in the context of

medicine development. Moreover, *co-creation* as an overarching core attribute of PE in medicine development further underscored that PE shares a theoretical core with SDL, VCC and VBM theories, which all claim that patients, as customers and experts, are always considered as value co-creators through their interactions with HCPs (M. M. Brown & Brown, 2013; Prahalad & Ramaswamy, 2004; Vargo & Lusch, 2004).

Furthermore, the present study suggested that the predicted core consequence of the concept of PE in medicine development is *improved value*, referring to the positive benefits for all healthcare stakeholders, in terms of improved patient value, improved healthcare value and improved business value, that PE in medicine development is thought to bring. These expected consequences of PE in medicine development resonate with the theoretical claim from a VBM perspective that improved patient value should determine the rewards for all healthcare stakeholders (G. C. Brown et al., 2003; Porter, 2010).

Finally, the development of a PE framework with aligned value and methodology was identified in the present study as a major influencing factor on the concept of PE in medicine development. Accordingly, a conceptual framework for PE in medicine development developed from the present study was presented (see ***Figure 10***) and discussed in relation to this identified knowledge gap. Moreover, a final definition of PE in medicine development from a value-creation perspective was proposed, based on the findings from the present study (see ***Table 15***). The conceptual framework and theoretical propositions for PE in medicine development (see ***Figure 11***) presented in this chapter offers a holistic account of this PE phenomenon in medicine development and provides novel insights into the theoretical core of this concept, thus addressing RO3 of the present study.

7 Discussions and conclusions

7.1 Introduction

In this chapter, the key findings from the present study are discussed, and further interpreted in relation to the research questions (RQs) (see Section 1.2) of the present study:

- RQ1: What does the concept of PE in medicine development mean?
- RQ2: How are PE in medicine development understood and perceived by key healthcare stakeholders?
- RQ3: How can PE in medicine development be conceptualized from a value-creation perspective?

The broader aims of the present study – to provide theoretical clarity on the concept of PE in the context of medicine development, and guide practice – have been addressed by the following outcomes:

(1) The development of a final definition of the concept of PE in the context of medicine development from a value-creation perspective with input from stakeholders, thus setting up the foundational basis for this concept.

(2) The development of a final thematic map about the antecedents, attributes, consequences and influencing factors of PE in medicine development by integration of stakeholder perspectives and literature, thus providing an in-depth and comprehensive contemporary understanding of this concept.

(3) The development of a conceptual framework of PE with theoretical propositions in the context of medicine development from a value-creation perspective, based on the above understandings, thus offering a theoretical interpretation of the PE phenomenon in medicine development.

In this chapter, the findings from the present study are further discussed within the current body of knowledge. The contributions of the present study to both theory and practice

are articulated, together with the novel insight gained and its relevance to the research issues, and the implications for the further advancement of the concept of PE in medicine development in theory and practice. Final consideration is given to the strengths and limitations of the present study and suggested future research.

7.2 Research contributions to theory

With the insight gained from the present study, the next sections revisit the study results and link them to the knowledge gap found (Section 1.1), the research questions (RQs) defined (Section 1.2), and the initial theoretical perspectives (Section 2.5) adopted for the present study. Taking these elements into consideration, answers to the RQs are articulated. Thereby, the present study's contribution to knowledge is discussed in the context of the current body of knowledge.

7.2.1 RQ1-What does the concept of PE in medicine development mean?

A major outcome from the present study is the final definition of the concept of PE in the context of medicine development (see ***Table 15***), built on a synthesis of current theoretical understandings of this concept (Chapter 4) and practical meanings given by interviewees (Chapter 5). A consensus understanding regarding the concept of PE in medicine development was considered a critical knowledge gap in the current literature (du Plessis et al., 2017; Lowe et al., 2016; Pushparajah, 2018). Therefore, a clear definition of the concept of PE in medicine development, developed from a value-creation perspective with the involvement of relevant stakeholders represents a piece of original work, contributing to the current body of knowledge by filling this knowledge gap (see ***Table 2***).

Previous definitions of the concept of PE were mostly developed in healthcare service and clinical settings and focused on the optimization of healthcare delivery through improved interactions between patients and physicians at the point of care, thus

predominantly drawing on social justice and ethical perspective (see ***Table 3***). Within the context of medicine development, four previous studies offered partial understandings of the concept of PE in medicine development from different, narrow perspectives: (i) describing how to use PE in the optimization of clinical trial design and conduct with best practice examples but offering no theoretical development of this concept (Hoos et al., 2015); (ii) proposing a patient-focused drug development (PFDD) framework but without reference to theoretical foundations (Perfetto & Oehrlein, 2015); (iii) suggesting focus areas and potential benefits of PE in medicine development, aiming to stimulate increased PE in pharmaceutical companies, but offering no clear definition of PE or its theoretical cores in this context (Lowe et al., 2016); and (iv) identifying four priority areas for further actions to facilitate PE expansion in medicine development, but offering no link to theoretical considerations (Boutin et al., 2017). Nevertheless, all four studies highlighted the same research problem: current understandings of PE in medicine development are fragmented and inconsistent. Therefore, a clear understanding of the meanings of PE in medicine development (answering 'what' and 'how' questions) was suggested as a crucial knowledge gap demanding further research. Building on the recommendations of these scholars, the present study offered a holistic definition of the concept of PE in medicine development from a value-creation perspective, drawing on synthesized knowledge from both the literature and practice, and therefore achieving an aligned contemporary understanding of this concept among users (see ***Table 15***).

This novel PE definition acknowledges the multi-faceted meanings given to this new PE phenomenon in medicine development by the key stakeholders (i.e., patients, society, and PHARMA), consistent with the social constructivist stance adopted in the present study. Next, these stakeholder perspectives were woven together through the identified overarching core attribute of PE in medicine development (i.e., *co-creation*), which defines what PE in

medicine development is all about: it is the co-creation of improved value for patients and all healthcare stakeholders with the patient as value co-creator in this context. Drawing on the aligned emphasis on patient value by all healthcare stakeholders, this definition of PE offers a consensus understanding of this new phenomenon in the context of medicine development. It shares further a theoretical core with VBM, VCC and SDL perspectives through the core attribute of *co-creation*, thus providing an insightful theoretical interpretation of the PE phenomenon in medicine development, which was missing in the extant literature (see ***Table 2***). Additionally, co-creation with patients within PE in medicine development was described in many areas by interviewees with empirical examples (see Section 6.2.2).

Given the above discussions, the novel definition of PE in medicine development developed by the present study (see ***Table 15***) offers a piece of original work, enhancing theoretical clarity and elucidating the contemporary meanings of this emerging PE phenomenon in medicine development from a value-creation perspective, thus expanding the knowledge base by answering RQ1 of the present study.

7.2.2 RQ2-How are PE in medicine development understood and perceived by key healthcare stakeholders?

The present study offered a final thematic map of PE in the context of medicine development from a value-creation perspective (see Section 6.2 and ***Table 10***), delineating the antecedents, attributes, consequences, and influencing factors regarding PE in medicine development and their congruence with the theoretical perspectives based on VBM, VCC and SDL. This final thematic map concerning PE in medicine development provides a comprehensive account of the core themes regarding PE in medicine development, beyond a simple definition, grounded in data yet woven together to form a complete picture of this social phenomenon. This holistic view of PE as a complex social phenomenon offers insight

into how PE in medicine development is understood and perceived by key healthcare stakeholders (RQ2): it aims to generate improved patient value, healthcare value and business value for all stakeholders (i.e., the anticipated consequences of PE in medicine development). Furthermore, the paradigm shift to VBM in healthcare, and the new role of the patient as consumer and expert (i.e., the identified antecedents of PE in medicine development) require the integration of patient value into existing medicine development processes within PE. Thus, the final thematic map of PE in medicine development, developed with inputs from healthcare stakeholders, offered a comprehensive answer to the RQ2, thus delineating the current use and significance of this concept in practices, which is thought to transform medicine development practices in the coming years (du Plessis et al., 2017; Duffett, 2017).

Next, as discovered in the present study, a key research issue associated with the PE phenomenon in medicine development was that healthcare stakeholders often have different priorities and divergent value understandings of PE in medicine development (Carmen & Workman, 2017). Different value perspectives among healthcare stakeholders prevented the formation of a unified view of this PE phenomenon in the extant literature (Hahn et al., 2017; Marzorati & Pravettoni, 2017). Taking a social constructivist ontological stance, the present study was able to explore the diverse value perspectives of relevant stakeholders (i.e., patients, medicine developers and PE experts) who have practical knowledge and experiences of PE in medicine development. Exploring these diverse value perspectives and making them explicitly promoted a comprehensive understanding of this complex social phenomenon from a value-creation perspective, based on which a final thematic map regarding PE in medicine development was developed (see ***Table 10***), which delineates the multi-faceted characteristics of this concept and underlines the importance of taking an integrated approach to tackle the research problems from a social constructivist stance, such

as in the present study. The final thematic map (with defined themes, categories, and indicators at the level of patient, society, and PHARMA) concerning key aspects of PE in medicine development (see ***Table 10***) offers a first reference model for future testing of PE in medicine development to further enhance the theory development in this field.

Furthermore, practical meanings of PE in medicine development were articulated through an exploration of this phenomenon from a value-creation perspective based on VBM, VCC and SDL (see Section 6.2). First, driven by the shift towards a VBM paradigm in healthcare, with patients recognized as consumers and experts within the context of medicine development, PHARMA needs to re-emphasize patient centricity and adopt PE in its pharmaceutical medicine development processes. PE in medicine development is, therefore, becoming increasingly relevant and important because, within the new VBM paradigm, achieving high patient value is the declared overarching goal that unifies and rewards all healthcare stakeholders including PHARMA (G. C. Brown et al., 2003; Porter, 2010). Consequently, PHARMA needs to integrate patient value within PE into its medicine development processes in response to this paradigm shift. Secondly, from a VCC and SDL theoretical perspective, the notion of the patient as a value co-creator in their health has been widely established in the healthcare domain, with an emphasis on partnership and collaboration as core attributes within PE at the societal level. Thus, the integration of patient value in medicine development was a logical next step within PE in medicine development at the PHARMA level because medicine development activities at PHARMA exist to serve patients and healthcare (Boudes et al., 2018; Boutin et al., 2017). Additionally, the present study delineated the practical relevance of the concept of PE in medicine development through rich accounts of empirical experiences from stakeholders, which offered examples of the significance and practical meanings of this concept in practice.

Accordingly, the practical meanings and perceptions of PE in medicine development by stakeholders can be illustrated by the paradigm shift to VBM, which requires the integration of patient value in medicine development through co-creation with patients, to deliver improved value for patients and all healthcare stakeholders (see Section 6.2). Hence, the final thematic map for PE in medicine development, developed with inputs from relevant stakeholders in the present study (***Table 10***), offers answers to RQ2 of the present study.

7.2.3 RQ3-How can PE in medicine development be conceptualized from a value-creation perspective?

The present study offered a PE conceptual framework with theoretical propositions in medicine development from a value-creation perspective (see ***Figure 11)***, which was developed based on interviews with key stakeholders and interrogated with literature (see Section 6.4). The PE conceptual framework offers a theoretical foundation that answers the questions of what PE in medicine development is about, what value PE in medicine development is expected to deliver and for whom, and how value can be co-created within PE in medicine development from a value-creation perspective, thus providing a theoretical development for PE in medicine development. As discussed in the literature, little conceptualization, and theoretical development of PE in medicine development was suggested as a critical knowledge gap, which prohibited the wide application of this concept in the practices (see Chapter 1 and ***Table 2***). Drawing on a social constructivist ontological stance, the present study was able to make the value-creation of PE in medicine development for key stakeholders explicitly on the one hand and unify these diverse value perspectives based on patient value as the declared overarching goal of all healthcare stakeholders on the other. Adopting a social constructivist ontological view in the present study proved effective to address the research issues, because it allows diverse value perspectives to be integrated

within a holistic conceptual framework which illustrates the attributes, antecedents, and consequences of PE in medicine development for key healthcare stakeholders.

Furthermore, theoretical propositions regarding PE in medicine development, developed from a VCC perspective and the insights gained in the present study (see ***Table 16***), provide advanced theoretical clarity to the concept of PE in medicine development, which offer further an initial set of hypotheses for future empirical testing of this concept, to advance the concept of PE in medicine development in theory and practice. In particular, the developed theoretical propositions of PE in medicine development in the present study have added knowledge regarding how value can be co-created by PE in medicine development from a VCC perspective, thus offering further guide for effective implementation in the practice. Hence, the developed PE conceptual framework and theoretical propositions offer answers to the RQ3 of the present study.

7.2.4 Theoretical clarity of the concept of PE in medicine development

Concept development can help investigate a social phenomenon by addressing areas of vagueness and ambiguity, thus resolving some of the pressing conceptual problems in the discipline (Bryman, 2015; Creswell, 2017). Although the term PE has been widely used in the context of medicine development by multiple stakeholders over decades, differing understandings of this concept remained, with little conceptualization found in the extant literature (Domecq et al., 2014; Frank et al., 2015; Higgins et al., 2017). Following Rodgers' (1989) approach, a concept development with input from the relevant stakeholders, conducted in the present study from a social constructivist stance, proved effective in offering an in-depth and comprehensive understanding of this complex social phenomenon, thus enhancing theoretical clarity of the concept of PE in medicine development.

The theoretical clarity of a concept is delineated through its clearly defined attributes, a thorough understanding of its contextual relevance (i.e., its antecedents, consequences,

surrogate terms, related concepts and implications) and a degree of coherence in relation to the overall theoretical framework (Duncan et al., 2007; Penrod et al., 2005; Rodgers & Knafl, 2000). In the current literature, little evidence was found about the attributes, the contextual relevance or the theoretical cores associated with the concept of PE in medicine development, despite the widely uncritical use of this concept in practice (Boutin et al., 2017; Higgins et al., 2017; Hoos et al., 2015). The present study made original contributions to enhancing the theoretical clarity of PE in medicine development, through offering (i) a final definition of PE in medicine development, based on its identified core attributes (see ***Table 15***); (ii) a final thematic map of PE in medicine development, developed through a comprehensive exploration of the contextual relevance of this concept (see ***Table 10***); and (iii) a PE conceptual framework in medicine development with a set of theoretical propositions based on the above understandings and novel insight (see ***Figure 11***).

Furthermore, the initial theoretical perspectives based on VBM, VCC and SDL, adopted for the present study (see Section 2.5), proved powerful for exploring the PE phenomenon in medicine development from a value-creation perspective (see also discussions in Section 6.3). From these theoretical perspectives, SDL and VCC shed light on the new PE phenomenon with well-established marketing and management principles (Prahalad & Ramaswamy, 2004; Vargo & Lusch, 2004) whilst VBM, as a new theoretical paradigm in the healthcare discipline, offered a contextual perspective to understand PE in medicine development. Moreover, the identified attributes of PE in medicine development from the present study (i.e., 'the patient as value co-creator'; 'integration of patient value'; and 'partnership and collaboration') demonstrated strong logical congruence with the theoretical cores of the SDL, VCC and VBM theories (see Section 6.3), thus further enriching these theories by adding new insights and expanding areas of application. In addition, the research methodological framework based on Rodgers' (1989) approach (see

Table 5) proved effective in addressing the research problems in the present study through the triangulation of data from the literature and interviews, which created a profound account of the PE phenomenon in medicine development, supported by different data sources and multiple perspectives, thus enhancing the trustworthiness of the study results.

Finally, the theoretical propositions associated with the concept of PE in medicine development, as developed from a VCC perspective in the present study, offered advanced theoretical clarity about how value can be co-created within PE in medicine development, which added an original contribution to the extant body of knowledge. Moreover, these theoretical propositions offered a first set of hypotheses for future empirical testing and further theoretical development of the concept of PE in medicine development.

Taking the above arguments together, the present study offers novel insight into the concept of PE in the context of medicine development. This is the first study to provide both theoretical and empirical knowledge about PE in medicine development from a social constructivist stance and a value-creation perspective, thus enhancing theoretical clarity and expanding the knowledge base in this field.

7.3 Practical implications and recommendations

The present study revealed that PE in medicine development was based on the theoretical foundation that VBM paradigm requires the presence of patient value in the medicine development life cycle (see Section 6.4). The practical implications of this PE proposition could be far-reaching and multiple for medicine development practitioners (see also discussion in Section 6.2.4):

(i) More studies may be necessary to collect these patients' voices throughout the medicine development processes, and this may increase clinical development complexity and cost at the PHARMA level.

(ii) Methodology regarding how to collect patients' voices through PE, and their use in regulatory reviews, would need to be clarified by the regulators to establish frameworks and incentives for PHARMA operations in medicine development at the society level.

(iii) Patients' capability to offer a science-based patient voice beyond anecdotes is necessary to have an impact on medicine development practices at the patient level.

Furthermore, the core PE propositions derived in the present study suggested that PE in medicine development is not simply a task that PHARMA needs to pursue; rather, it is a multi-factorial ecosystem which demands the convergence and collaboration of all healthcare stakeholders at multiple levels of society, patients and PHARMA, thus further strengthening the need for co-creation of patient value through the partnership and collaboration of all healthcare stakeholders (i.e. identified key attributes of PE in medicine development). The necessity for partnership and collaboration of all stakeholders within PE in medicine development became still more evident in the interviewees' appeals for a master PE framework with aligned methodology and processes to guide effective PE application in practice (see Section 6.3). This is only possible through partnership and collaboration of all actors within PE in medicine development, identified as a key attribute of the concept of PE at the society level in the present study. Drawing on the above advanced understandings of the concept of PE in medicine development, practical implications and recommendations for healthcare stakeholders are elaborated upon and proposed in the next paragraphs.

(i) Recommendations for patients and patient organisations

VBM suggests that value is determined by the patients – the beneficiaries of medicine development (Section 2.5.1). Following a VBM perspective, patient value should determine the underlying value proposition of a potential medicinal product throughout the medicine development life cycle and serve as a common denominator unifying the interests of all healthcare stakeholders within PE in medicine development (Porter, 2010). Increasingly, the regulators' requirements for the presence of patients' voices in product review and approval processes are having a huge impact on the established medicine development processes of PHARMA (Duffett, 2017). As a result of these new regulatory requirements, PHARMA needs to integrate patient value within PE in medicine development, to fulfil regulatory requirements but also – most importantly – to meet patients' needs and expectations (Kelly et al., 2015). Consequently, patient value will decide the ultimate market success of a medicinal product, and patients and patient organisations (POs) will take an increasingly active role within PE in medicine development (see Section 6.2).

POs play an important role in enabling patients' voices to be heard and integrated into the established medicine development processes of PHARMA. Given that patients' health literacy and capability for advocacy were suggested to be key prerequisites for successful PE in medicine development, but were also found currently as a key barrier at the patient level, POs are expected to build up patients' collective capability to facilitate PE in medicine development in the following areas (see discussion in Section 4.3.2):

(i) Educating and training patient experts for PE participation

(ii) Defining methods of how to incorporate patient input via PE

(iii) Enhancing PE through collaboration with patient organisations

These recommended activities, supported by POs at the patient level will facilitate the gathering of a science-based, collective patient voices which is believed to have greater

impact on medicine development and approval processes (see Section 6.2.4), as illustrated by an interviewee from a patient organisation:

> *We are offering training to our communities to build up their capacity to advocate themselves; and we also train patients to understand research and the impacts of research on public health and to enable them to step in as co-investigators, stakeholder engagement advisors. Within the process of capacity building, we also involve stakeholder engagement advisors and patient co-investigators to further build up and share the power with the community.* [P-12 (PX)]

This interviewee elucidated the importance of the systematic training of patients to build up their capability as co-investigators and advisors, to fulfil the new role expected of patients within PE in medicine development. Worldwide, different POs are continually emerging to support this capacity-building activity and establish patient research networks on a global scale (EPF, 2013; EUPATI, 2016a; NHC, 2016). Drawing on the above discussions, recommendations to patients and patient organisations to advance PE in medicine development at the patient level are proposed and summarized in ***Table 17***.

(ii) Recommendations for policy and healthcare authorities

The present study raised awareness that PE in medicine development is a multi-faceted social phenomenon that requires a holistic approach, based on aligned value understandings and the collaboration of patients, PHARMA and healthcare decision-makers (see Section 6.3). Particularly, a clear PE method and process framework specifying regulatory requirements regarding PE in medicine development were deemed urgently needed and impactful, to create incentives and provide guidance for meaningful PE implementation in medicine development practices (see Section 6.2.4).

Furthermore, the present study revealed that PE in medicine development was based on the proposition that VBM requires the presence of patients' voices in medicine development processes (see Section 6.4). Following this principle, expectations, and requirements of patients and HTA agents, who are predominantly concerned with patient value and healthcare value in the context of medicine development, will become increasingly important and relevant in medicine development processes. Therefore, collecting an aligned value dataset describing patient value and healthcare value associated with the medicine to be developed is essential in medicine development processes within PE (see Section 6.2). In this regard, policymakers and health authorities have an important role to play in setting up a master method and process framework to guide PE implementation in practice (DIA, 2017; PFMD, 2018a; IMI, 2018). Below are the recommendations for this stakeholder group derived from the present study (see discussions in Section 6.2.4):

(i) Define a PE method and process framework based on aligned value

(ii) Define an ESL framework for PE in medicine development

(iii) Define incentives for PE in medicine development, aligned with patient value

(iv) Create an evidence base for the benefits of PE in medicine development

In particular, the development of core-outcome-sets based on the aligned value of healthcare stakeholders within a master PE method and process framework was considered to be a crucial future step in informing the effective application of PE in medicine development practices. This was identified as both a knowledge gap and a critical influencing factor calling for future research to advance PE in medicine development practices at the society level (see Section 6.2.4). Arguments supporting this recommendation were also offered by interviewees, for example:

> *I think this Core-Outcome-Set development is a good idea to resolve the mismatch of expectations of all relevant stakeholders – regulators, HTA, patients and PHARMA. It ensures an optimal clinical trial design to fulfil the requirements of decision-makers and meet the patients' expectations for acceptance. With this concept, the inputs from HTA and patients are brought into the clinical trial design at an earlier stage instead of being considered sequentially after regulatory drug approval.* [P-26 (PT)]

This interviewee touched on the most critical area to be addressed by policymakers and health authorities regarding PE in medicine development: alignment of core-outcome-sets, reflecting the aligned values of all stakeholders (concerning efficacy, safety, HRQoL, PRO parameters), to guide integrated data generation in medicine development processes within PE. The establishment of norms, methodology and core-outcome-set requirements by policymakers and HAs would have a strong impact on the convergence of effort and effective implementation of PE in medicine development practices and was, therefore, recommended by the present study for the advancement of PE in medicine development at the society level (summarized in ***Table 17***).

(iii) Recommendations for PHARMA

Co-creation of value for patients and healthcare within PE in medicine development demands a partnership and collaboration model between HCPs and patients (and/or patient organisations) throughout the medicine development lifecycle (i.e., through interactions in co-prioritisation, co-planning, co-implementation, co-dissemination and co-measurement) (see Section 7.2.3). This implies a significant change to medicine development practices, moving away from a charity model in which resources, knowledge and decisions are almost all on the provider side, to a partnership model, in which all social and economic actors

become resource integrators, sharing knowledge and making shared decisions towards common goals (Boutin et al., 2017; Dewulf, 2015). This practical implication is also in congruence with the key principles of SDL that customer is always a co-creator of value, and all social and economic actors are resource integrators (Vargo & Lusch, 2004).

While the moral imperative regarding 'why PE is necessary in medicine development' has been recognized, operational barriers preventing effective PE in medicine development at the PHARMA level remain to be overcome (see Section 6.2.4). Drawing on understandings from the present study, the following practical recommendations are proposed to PHARMA who want to implement PE in medicine development processes effectively (see discussions in Section 4.3.3, Section 5.3.5, and Section 6.2.4):

(i) Establish a patient-centric culture and design PE processes integrated into existing medicine development practices
(ii) Design a PE method and process framework based on aligned value with multiple stakeholders
(iii) Define PE measurement metrics and generate evidence of PE outcomes
(iv) Demonstrate the link between PE in medicine development and business success
(v) Collaborate with patient organisations through partnerships
(vi) Establish trust, equality, respect, co-learning and transparency in a reciprocal partnership between PHARMA and patients

These are the consolidated recommendations, derived from the final integrated analysis of the literature and interviews, which may guide PHARMA in the effective implementation of PE in medicine development practices and capture its potential benefits. Particularly, conducting authentic, patient-centric PE in medicine development was

suggested as a powerful mechanism to establish trust, respect, co-learning, transparency and a reciprocal partnership between PHARMA and patients (see Section 4.3.3). This aspect was endorsed by interviewees to be even more important than the expected tangible benefits associated with PE in medicine development for PHARMA, as illustrated below by one interviewee:

> *What we want is the intrinsic motivation of the PHARMA researchers who believe that my work will become more open and interesting if I collaborate with the patients, and, at the end of the day, I will profit from the PE that I am doing. And here the reward should also be the intrinsic motivation because PE is important to you. That is something which should be part of the culture and policy of the researcher's own PHARMA company and/or research institution*. [P-16 (PX)]

This interviewee emphasizes the intrinsic motivation that PHARMA should have in its PE endeavours in medicine development: PHARMA should embrace PE in medicine development not only for financial and business reasons, but because it will deliver improved patient value and healthcare value, the primary goals of PE in medicine development. This requires PHARMA to rethink its current medicine development practices and, most importantly, to adopt an authentic patient-centric attitude in setting up a trustful, co-creating partnership with patients and other stakeholders within PE (see ***Table 17***).

Table 17: Practical recommendations regarding PE in medicine development

(i) Recommendations to Patient and patient organisations	(ii) Recommendations to Policy and healthcare authorities	(iii) Recommendations to Pharmaceutical companies
(i) Educate and train patient experts for PE participation (ii) Define methods of how to incorporate patient inputs in medicine development by PE (iii) Enhance PE in medicine development through collaboration and partnership with stakeholders	(i) Define PE method and process framework based on aligned value with stakeholders (ii) Define ESL framework for PE in medicine development (iii) Define incentives for PE in medicine development - aligned with patient value (iv) Create evidence base demonstrating benefits of PE in medicine development	(i) Establish patient-centric culture and design PE processes integrated into existing medicine development practices (ii) Design an aligned PE methods and process framework based on aligned value with multiple stakeholders (iii) Define PE measurement metrics and generate evidence of PE outcomes (iv) Demonstrate link between PE in medicine development and business success (v) Collaborate with patient organisations through partnerships (vi) Establish trust, equality, respect, co-learning, transparency and reciprocal partnership between PHARMA and patients.

7.4 Strengths and limitations

In this section, the research methods, processes and findings of the present study are subjected to critical reflection in respect of the trustworthiness of qualitative research such as this (i.e., credibility, transferability, dependability and conformability) (as discussed in Section 3.7). Next, the contributions of the present study are discussed within the context of current body of knowledge, and considerations are given to the researcher's personal reflexivity along the research journey. Furthermore, the strengths and limitations of the present study are reflected, guided by the quality criteria for qualitative research offered by Elliott, Fisher & Rennie (1999) and the specific quality appraisal framework for good thematic analysis provided by Braun and Clarke (2013) (as discussed in Section 3.7).

Credibility

Credibility concerns the internal validity of research, how believable the findings are (Bryman, 2015). The present study provides greater theoretical clarity about the meanings, contextual factors, and theoretical cores of the concept of PE in medicine development (see

Section 7.2.4). A critical literature review (Chapter 2) presented the current knowledge base, theoretical assumptions, research issues and knowledge gaps associated with PE in medicine development and informed the development of the research objectives and questions, the initial theoretical perspectives, and the research methodology framework, defined as a foundation to address the research issues (Chapter 3). The present study adopted the evolutionary concept development approach by Rodgers (1989) and started with a systematic, multi-disciplinary literature search of publications regarding PE in medicine development. Literature appraisal and eligibility checks applied to the retrieved publications established a qualified literature database (see ***Figure 4***). The inclusion of high-quality literature in the thematic analysis in the present study ensured that the study findings drew on reliable evidence, thus strengthening the analytical claims and credibility of the study results (Robson, 2002).

First, thematic analysis of the literature proved effective in developing a provisional thematic map of PE in medicine development (see ***Figure 8***), which was grounded in literature data and guided by the initial theoretical perspectives based on VBM, VCC, and SDL. Within this process, a detailed description of the methods used in the transcription, coding and analysis procedures was offered (see Section 3.5.1 and Section 3.6.1) and the developed coding book was presented (see ***Annex 8***) to support other researchers in replicating the research processes for further investigation of this PE phenomenon. However, a limiting factor in this process was that only publications in the English language were searched and retrieved; it may be that literature in local languages was omitted. Nevertheless, considering the number of literature samples included (n=156) and the comprehensive international perspectives offered by these publications, the impact of this limiting factor is considered minimal to the study result.

Next, in the fieldwork phase, in-depth semi-structured interviews with relevant PE stakeholders were conducted, with the aim of capturing the meanings and practices of PE in medicine development from the practitioners' perspectives. A purposive sampling method was applied to ensure the recruitment of interviewees with relevant experience and knowledge within the research domain. This recruitment strategy proved effective in finding 32 interviewees from diverse backgrounds with a broad international coverage (see Section 3.5.3). Ethical considerations were followed and respect for the participants was ensured through informed consent forms and responsible data-handling processes by the researcher throughout the study. An interview guide was designed to support the exploration of research questions, which proved effective for the purpose of the inductive conceptualization of the PE phenomenon based on the experiences of participants that brought novel insight. A detailed description of the recruitment strategy, interview guide, participant information sheet, informed consent form and research ethical approval are included (***Annexes 2–7***), providing full transparency about the methods and processes employed in the present study. Moreover, thematic analysis proved effective in the analysis of interview data, which led to the development of a second PE thematic map (***Figure 9***) with coding book (***Annex 9***) based on insights gathered from the interviewees. Insights gathered from multiple perspectives, reflecting the diversity of the relevant PE stakeholders, enhance the credibility of the study findings grounded by empirical data (Braun & Clarke, 2013). However, some limitations should be acknowledged. Qualitative research in general, such as in the present study, is dependent on the experiences and perspectives of study participants on a specific topic, but the researcher cannot control aspects of the environment that may have influenced the perspectives of the study participants (e.g., the healthcare system in the country where the participant is living, the participants' organisation and their specific role in their organisation). Nevertheless, the diversity and subjectivity of study participants is positively

valued in a qualitative paradigm which allows a rich and comprehensive understanding of a complex social phenomenon such as PE in medicine development, thus enhancing the credibility of study findings. Taking into consideration the diversity and subjectivity of participants is congruent with the social constructivist stance of the researcher, who believes that meanings are constructed by individuals through social actions, and that conscious interpretations construct the meanings of the social phenomena which are continually shaped by social actors (Bryman, 2015; Burr, 2003). Consequently, an inductive thematic analysis of the interviews proved effective both for the conceptualization of PE through showing the whole picture, and for generating insight into the PE phenomenon by preserving the narrative nuances grounded in the rich accounts of interviewees, thus enhancing the coherence and credibility of the study results (Elliott, Fischer & Rennie, 1999).

In the final analysis phase, the themes generated from both the theoretical and fieldwork phases were triangulated, leading to the development of a final PE conceptual framework in medicine development (see ***Figure 10***), together with a PE definition (see ***Table 15***) and a set of theoretical propositions (see ***Table 16***). The triangulation of data from different sources (literature and interviews) and perspectives (interviewees with diverse backgrounds) proved effective in offering a holistic yet in-depth account of PE in medicine development. Triangulation strengthened the analytical claims and allowed a richer and fuller story of the PE phenomenon in medicine development, thus enhancing the credibility of the study results (Webb et al., 1966). As a result, the final integration of the themes derived from the theoretical and fieldwork phases informed the development of a conceptual framework for PE in medicine development with a set of theoretical propositions (see ***Figure 11***), addressing a critical knowledge gap in the extant literature (Hoos et al., 2015; Perfetto et al., 2015), and thus enhancing theoretical clarity of the concept of PE in medicine development.

Nevertheless, consideration should be given to the potential subjectivity of the researcher in the data interpretation and analysis, which may be influenced unconsciously by the researcher's own values, assumptions, anticipations, and experiences. Although qualitative research is understood as a subjective process, we cannot leave the researcher's subjectivity out completely (Braun & Clarke, 2013). Aware of potential bias and its impact on the research processes and results, complete transparency was offered throughout the research processes. A rigorous audit trail of the data analysis and decision-making was maintained, recorded in the NVivo system. Furthermore, the research procedures and findings were regularly discussed with two academic supervisors, which may serve as peer review to ensure transparency and avoid researcher bias to the maximum extent possible, thus enhancing the credibility of the present study.

Transferability

Transferability concerns the external validity of research, i.e., whether the results from the study can be generalized from the sample to a wider context. Given the emphasis in the present study on multiple realities from a qualitative, interpretivist and social constructivist stance, it was more relevant to consider the ecological validity of a qualitative study, which is concerned with the relationship between the real life and research settings (Braun & Clarke, 2013). In the present study, most interviews (over 70%) were conducted through Skype due to distance constraints, although all these interviewees were situated in their natural environment where they should feel safe and comfortable to have a free conversation. However, the interview settings might not be considered as a fully real-life situation, albeit qualitative research in general 'tends to be seen as less removed from the real world than quantitative measures' (Braun & Clarke, 2013, p. 280). Furthermore, qualitative researchers are encouraged to provide a rich and thick description of the context to convey the findings and offer multiple perspectives on a theme (Lincoln & Guba, 1985).

In so doing, they may transport a shared experience to the readers, to help others to judge the transferability in other contexts (Bryman, 2015). Following these considerations, a comprehensive account of the changing healthcare and medicine environment, which is the contextual basis for the concept of PE in medicine development, was offered (Section 2.3 and Section 2.4). This facilitated a common understanding with the readers about the context and background of the PE phenomenon in medicine development and, thus, enhanced the transferability of the research findings from the present study.

Dependability

Dependability refers to the reliability of a qualitative study in terms of whether the research findings are likely to remain applicable over time, indicating the consistency of the research across projects (Bryman, 2015). However, reliability is considered as rooted in a realist view of a single external reality (Creswell, 2017), which is therefore less relevant for qualitative research based on the social constructivist stance of the researcher who views knowledge as socially constructed, context-bound and historically shaped. Consequently, knowledge is considered to be continually shaped by social actors and, thus, there is no single truth independent of context and time from a social constructivist stance (King & Horrocks, 2010). Nevertheless, consideration was given to the dependability of the methods used in the data collection and analysis as a broader version of reliability in qualitative research (Bryman, 2015). The present study offered complete transparency and great details about the research methods throughout the research processes and, thus, enhanced the method dependability for other researchers to replicate or to conduct a similar study at other times.

Confirmability

Confirmability is concerned with whether the researcher has allowed their own values, assumptions, and experiences to intrude, although complete objectivity is not possible in qualitative research (Kvale & Brinkmann, 2009). In the present study, the researcher's theoretical assumptions, research methods, epistemological position and role in the study were made as explicit and transparent as possible to the readers, to minimize potential researcher bias (see Chapter 3). Wherever possible, the researcher established the meanings of the research phenomenon from the perspectives of participants and data and maintained constant reflexivity and neutrality as an outside observer throughout the study, thus enhancing the confirmability of the research results.

Nevertheless, the methodology limitations in the present study should be discussed. Firstly, the concept analysis approach has frequently been criticized in literature as a weak method, allowing the uncritical use of a framework without a clear ontological stance (Duncan, Cloutier, & Bailey, 2007) and lacking in depth, rigour and replicability to support theory-building (Beckwith, Dickinson, & Kendall, 2008; Risjord, 2009). In contrast to the above criticisms, the present study presented and justified a clear epistemological position (interpretivist) and ontological stance (social constructivist) at the start of the study. The research paradigm taken by the researcher informed the selection of Rodgers' (1989) evolutionary concept development approach, which was considered in congruence with the researcher's philosophical paradigm. Secondly, Rodgers' (1989) evolutionary approach emphasizes great rigour in data sampling and analysis to generate in-depth insights from the data, and this was evidenced as a valid method by an increasing body of literature (Doyle, 2008; Poortaghi et al., 2015; Sofronas, Wright & Carnevale, 2018; Tofthagen & Fagerstrom, 2010; Weathers, McCarthy & Coffey, 2015). Additionally, an exhaustive, systematic literature search was performed for the thematic analysis of the literature in the theoretical

phase of the present study, which demonstrated even more rigour and depth than the literature sampling method proposed by Rodgers (1989) (see Section 3.5.1). Lastly, the appeal for replicability in concept development by some critics (Beckwith, Dickinson & Kendall, 2008; Penrod & Hupcey, 2004) was rooted in a realist ontology (Beecher et al., 2017; Duncan, Cloutier & Bailey, 2007) which was, therefore, considered not in congruence with Rodgers' (1989) evolutionary approach or the researcher's own research paradigm and, thus, not relevant in evaluating qualitative research such as in the present study.

Next, the limitations associated with the thematic analysis method, as applied in the present study, should be recognized. Despite its frequent use as a data analysis method in qualitative studies, several issues associated with it have been discussed by scholars: (i) the potential bias of the researcher; (ii) issues in making sense of the data to support analytical narratives beyond the description of themes; (iii) the potential mismatch between data interpretation and theoretical framework; and (iv) the quantification of sources and references in thematic analysis processes for the identification of themes and patterns (Gibson & Brown, 2009; Javadi & Zarea, 2016). These potential pitfalls associated with qualitative, thematic analysis were consciously mitigated by the following measures in the present study, aiming to ensure a data-driven inductive analysis, yet telling a convincing story about the data, through a balance of analytic narrative and illustrative interview extracts, as recommended by Braun & Clarke (2013):

(i) Regarding avoidance of potential researcher bias: comprehensive reflections were discussed, and mitigation measures undertaken in the present study, as discussed in the above paragraphs concerning the trustworthiness of this study.

(ii) Regarding making sense of data beyond the description of themes: an initial theoretical perspective defined at the beginning of the present study (Section 2.5) provided an analytical lens for the data analysis and sense-making, which proved

effective in combining the datasets into a coherent analytic account of the meanings of the data. The constant interrogating between analytical claims and data extracts throughout the theoretical, fieldwork and final analysis phases in the present study (as presented in Chapters 4–6) ensured that analytical accounts and data extracts were matched and supported each other.

(iii) Regarding the potential mismatch between the data interpretation and theoretical framework: in the present study, inductive qualitative coding was applied to both the literature and interview data. This approach has the advantage of generating themes inductively, to ensure that identified themes and patterns are grounded in data yet guided by the initial theoretical perspectives as a lens. For instance, the interview guide (***Annex 2***) was developed based on the research questions (Section 1.2) and the research methodology framework (Section 3.4), which offered a consistent framework for data collection, interpretation and the generation of new insights that combined to form a whole picture. Additionally, themes emerging from the literature and interviews were constantly analysed regarding their relation to the research questions and the theoretical perspectives to check consistency and coherence.

(iv) Regarding quantification of sources and references in a qualitative thematic analysis study: counting of incidence frequency of terms was applied in the thematic analysis processes in the present study to support the identification of core themes and patterns, which may seem odd in a qualitative data analysis. However, the quantification of the repetition of specific terms proved effective and efficient in handling a huge dataset in a qualitative study (Boyatzis, 1998). In the present study, 648 sources with 3,619 references were generated in the theoretical phase through the thematic analysis of the literature data, and 211

sources with 1,647 references were generated in the fieldwork phase through the thematic analysis of the interviews. It would be almost impossible to handle such a large amount of data without the support of the NVivo system which offers, besides the repetition counting of terms, useful analysis tools (such as *query* and *explore*) to support the researcher in identifying patterns and relationships among codes and themes. Consequently, incidence-counting with the support of NVivo proved helpful in supporting the thematic analysis processes of qualitative data analysis in the present study. However, these analysis tools embedded in the NVivo system can only support the exploratory eyes and analytic mind of the researcher (Bazeley & Jackson, 2013). Making sense of the data and producing convincing narratives linked with the data is the role of the researcher, who should not merely pay attention to the repetition of terms but, rather, explore meanings and patterns to generate convincing analytical claims which the data tells (Braun & Clarke 2013). Therefore, quantification of data sources supported but did not replace the analytical work of the researcher and hence, they proved complementary to each other and supportive of a qualitative research such as that in the present study.

Next, consideration was given to the sample size and its contribution to knowledge-building in the present study. In total, 156 literature (published between 2012 and 2019) and 32 interviews were included in the final integrated analysis. Core themes developed from different data sources were suggested as having reached saturation point through the comprehensive interrogation of 859 data sources with 5,266 references (see ***Annexes 8–10***). This large dataset offered a strong evidence base for the analytical claims made in the present study and contributed to the credibility of the study findings.

Furthermore, my professional identity as developer of medicine working in a pharmaceutical company was reflected comprehensively within the wider research process in the present study (see Section 1.3; 3.2; 3.4; 3.6; 3.7; and 3.8) to provide complete transparency and minimise potential bias. At the outset of my research journey, I presumed that PE in medicine development is a means employed by PHARMA to polish their public image. Experiencing the lack of PE arising in the realities of medicine development (as a conventional medicine developer), my scepticism about the real value of PE in medicine development further drove me to explore the PE phenomenon from a value-creation perspective. Motivated by my curiosity in this field, it was a natural decision for me to search for answers in the literature and from experts (via interviews) to establish the understandings of this concept inductively through an integration of knowledge beyond my own existing knowledge, thus seeing myself as an external research instrument within this study. Moreover, recognizing PE in medicine development as a complex social phenomenon involving multiple stakeholders with diverse perspectives, inspired me to explore this phenomenon from a social constructivist ontological stance within an interpretivist epistemological paradigm. Adopting this research paradigm further guided me to develop the methodological framework, following Rodgers' (1989) conceptual developmental approach, to expand knowledge inductively based on the data and experiences of the interviewees. Therefore, my professional role as a medicine developer has motivated me to address the research issues from the outset but has not played a role in the methodological decisions for this study, which were informed by literature and research paradigm adopted to best address the research questions (see Section 3.2 and 3.4).

Finally, attention was given to my role as researcher in the present study. An outsider role was declared *a priori* both in the research methodology framework (see Section 3.4) and to the interview participants (see PIS in ***Annex 5***). Furthermore, thoughtful reflectivity

and caution were constantly applied to minimize potential researcher bias throughout the research. However, several aspects should be considered as part of my personal reflexivity throughout the research journey in the present study. At the beginning of this study, I believed that PE in medicine development was the sole responsibility of PHARMA, who should naturally embrace this concept because it was such a popular term cited by so many working in the medicine development domain. The only remaining challenge was to find a scientifically validated method to enact PE in medicine development. Obviously, with this belief at the outset, I was taking a positivist stance with a conventional reductionist attitude as a medicine developer working in the pharmaceutical industry, trying to simplify the research problem and remove it from the complexity of the real world. Over the course of the research journey, after taking a closer look at this concept through intensive interrogation with a significant amount of literature gathered in the present study, the multi-faceted and multi-dimensional characteristics of this social phenomenon started to emerge. I began to realize that taking a positivist stance was not appropriate in exploring a complex, new social phenomenon such as PE in medicine development. Rather, a social constructivist philosophical stance was deemed more suitable to get closer to the constructed multiple meanings given to this phenomenon by relevant stakeholders, although positivism is still the prevailing philosophical paradigm underlying the medicine development domain. This paradigm shift on my part through the research activities completely changed how the research issues were addressed and how the data were collected and analysed. Adopting a social constructivist stance for the present study helped me to listen to the data, appreciate the experiences and perceptions of the participants, and build a data-driven narrative framework. My research journey in the present study illustrated the iterative processes in searching for the most proper research paradigm and methodology to address the research problems. The research methodology framework adopted by the present study proved to be

appropriate to achieve insights through in-depth enquiry and integrated data analysis, while maintaining the nuances and richness grounded in the data. In doing so, the confirmability of the research results in the present study could be further enhanced.

7.5 Suggested future research

Based on the thematic analysis of the literature data, three major knowledge gaps concerning the concept of PE in medicine development were found (see ***Table 2***). The present study has addressed these identified knowledge gaps through offering the following study outcomes:

(a) a final definition of PE in medicine development (***Table 15***),

(b) a final thematic map about PE in medicine development (***Table 10***), and

(c) a conceptual framework for PE with theoretical propositions in medicine development (***Figure 11***).

This novel knowledge of PE in medicine development was generated with the involvement of the relevant PE stakeholders and interrogated with extant literature, thus offering a consensus understanding of the concept of PE in medicine development among the users. With the greater theoretical clarity offered to these critical research issues, the present study may serve as a foundational work for future researchers to further address the remaining critical research issues associated with the concept of PE in medicine development: (i) develop a master methodology and process framework combining the science-driven biomedical research with the patient-centric, value-driven PE approach in medicine development, and (ii) generate an evidence base to support the assumed positive benefits of PE in medicine development.

First, three key defining attributes of the concept of PE in medicine development were identified in the present study: (i) partnership and collaboration, at the society level; (ii) integration of patient value, at the PHARMA level; and (iii) patient as value co-creator at

the patient level, which were derived from the underlying thematic codes that can serve as indicators to test the presence of these identified attributes respectively (see ***Table 10***). Thus, these identified key attributes and associated indicators of PE in medicine development at the levels of patient, society, and PHARMA, offer an initial reference model for future empirical testing of the concept of PE in medicine development. Concept measurement and testing is argued as a crucial step for further concept development (Rodgers & Knafl, 2000).

Second, developing master PE method and process framework needs to follow a consensus understanding of the 'what and how' questions regarding PE in medicine development. With the new insights gained from the present study having answered these questions, the PE conceptual framework developed in the present study (***Figure 10***) provides a foundational platform for the future development of detailed integrated PE methods and processes, which were suggested as a pressing issue regarding the effective implementation of PE in medicine development practices.

Thirdly, issues remain regarding the lack of evidence to substantiate the positive benefits of PE in medicine development, but this can be fully understood only after the long-term effective implementation and measurement of PE in practice. For this purpose, the PE conceptual framework presented in the present study could serve as a foundation for future researchers to conduct empirical studies to test the relationships among the antecedents, attributes, and consequences of PE in medicine development, to generate empirical evidence in future research and address this knowledge gap.

Fourthly, the present study proposed a set of theoretical propositions associated with the concept of PE in medicine development from a VCC perspective (see ***Table 16***). These proposed theoretical statements concerning the concept of PE in medicine development offer a set of hypotheses for future empirical investigation by other researchers. Future testing of

these PE hypotheses may allow further theory development regarding PE in medicine development and expand knowledge in this field.

Lastly, the present study revealed that the concept of PE in medicine development shares the theoretical core of co-creation with SDL, VCC and VBM theories, which shed new light on this PE phenomenon from several disciplinary aspects (i.e. marketing, management, and healthcare). The theoretical perspectives based on SDL, VCC and VBM in the present study has proven their explanatory power in exploring a new complex social phenomenon – such as PE in medicine development – thus expanding the application areas of these theories into the new domain of medicine development. Building on the new insights gained from the present study, future researchers may refine and advance these theoretical perspectives with regards to their applicability, compatibility, and significance of applications in the real-life practice of PE in medicine development.

7.6 Conclusions

The present study aimed to promote clarity on the concept of PE in the context of medicine development, both in theory and practice. Throughout the research processes, greater insights were gained regarding the conceptual core of PE and the relevant contextual complexities surrounding this concept in the context of medicine development. Co-creation was identified as an over-arching core attribute of the concept of PE in medicine development, while patient centricity was identified as an over-arching core antecedent, and improved value as an over-arching core consequence of the concept of PE in this context. Furthermore, the new insight gained from the present study offered a deep and comprehensive understanding regarding the *what* and *how* questions of PE in medicine development from a value-creation perspective, thus addressing a critical knowledge gap in the extant literature.

Furthermore, the present study raised awareness that PE in the context of medicine development is a multi-faceted, complex social phenomenon, which requires an integrated holistic approach based on aligned value understanding and the collaboration of all healthcare stakeholders to make it a meaningful concept in real life. First, clear regulatory requirements including a defined PE method and process framework in medicine development was deemed to be urgently needed to guide meaningful PE implementation in practice. Secondly, taking an authentic patient-centric attitude within PE by PHARMA was suggested to be a key prerequisite for an effective PE in medicine development; and significant culture and process changes are demanded at PHARMA to live up to PE expectations. Thirdly, despite the widespread appreciation of the patient as a consumer and expert within the new value-based medicine paradigm, patients' health literacy and advocacy capability need to be systematically increased with the support of patient organisations, to offer a science-based patient voice in medicine development as a competent value co-creator.

Lastly, the new insight gained from the present thesis implies that partnership and collaboration are needed among all healthcare stakeholders, to advance PE in medicine development through further convergence of value perspectives of all stakeholders based on patient value throughout the medicine development lifecycle.

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Annex 1: Key literature findings regarding PE in medicine development

Literature	Study type	Key themes	Findings regarding PE in the context of medicine development
Messina et al., 2012	Empirical study	• PHARMA should include patient experience study in early medicine development; • Patient advocacy group can take active role to bring-in patients' voices; • Further development of transparent HTA processes to facilitate PE	A pilot study to form the basis of PE in the Health Technology Assessment (HTA): • HTA of medicine should incorporate patients' voice; • Industry can assist in acquiring patients' perspective in medicine development; • HTA should involve patient advocacy group to incorporate patients' perspective.
Carman et al., 2013	Scholarly article	• Patients are at the core of healthcare system; thus, patients need to become more active, informed, and influential in medicine development and decision making.	Propose a PE framework for understanding: • PE ranges from consultation, involvement, partnership, and joint-leadership; • PE can happen on individual, organizational, and societal levels.
Domecq et al., 2014	Systematic review	• Minimal theoretical or conceptual underpinnings concerning PE is available; • Little conceptual development of PE can be found in this field; • Science of PE needs to be advanced to demonstrate the value of PE and how to perform.	Assess best practices of PE in research: • PE in research is likely feasible; • But PE comes at a cost and can become tokenistic. • Research dedicated to identifying the best methods to achieve PE is lacking and clearly needed.
Kelly et al., 2015	Scholarly article	• Scientific methodologies in medicine development are largely laden with unacknowledged values; • Patient values and scientific evidence go hand-in-hand also in the biomedical research. • Research should investigate methods to elicit patient values and integrate them into scientific clinical research.	Demonstrate the value consideration can enhance every aspects of the evidence-based medicine: • Robust scientific findings are meaningless unless interpreted in the societal, cultural, and political context • Values are to be made explicit, systematically explored, and integrated into clinical research.
Hoos et al., 2015	Scholarly article	• In every industry, product development starts with understanding the customer's need and provide solution to meet this need; the same should be true for medicine development; • Routine PE in medicine development will lead to better outcome.	Contributions of PE in the R&D processes is discussed: • Setting research agenda; • Development of research questions; • Selection of outcomes and comparators; • Optimize recruitment; • Translation and dissemination of research findings; • A master PE framework is needed for industry-led medicine development.
Perfetto et al., 2015	Empirical study	• Patients as partners; • Continuous PE in medicine development lifecycle; • Meaningful PE with appropriate methods and processes; • The right patients are engaged; • The right time to engage patients; • The science of PE is still emerging, especially for medicine development.	Define the PE in the patient-focused drug development (PFDD): • PFDD is a formal process by which drug developers and regulators form a partnership with the patient to enhance drug development, research, regulatory, and reimbursement processes with the patient voice. This partnership engages patients to obtain as critical input their views, experiences, and preferences throughout a product's lifecycle.
Getz, 2015	Empirical study	• PE promotes the relevance, pragmatism, feasibility, and	Develop guiding principles for patient-centric PE in R&D:

		interactivity of the patient-centric clinical research.	• PE requires reasonable return-on-investment (ROI).
Frank et al., 2015	Theoretical research	• Proposed PE principles are reciprocal relationship, co-learning, partnership, trust, transparency, and honesty.	Develop conceptual model for patient-centred outcome research (PCOR) around: • Foundational elements; • Actions and behaviours involved; • Outcomes of the actions
Croft et al., 2015	Scholarly article	• Proposed key performance indicators (KPIs) in measurement of PE success: *PHARMA internal: strategy, capability, processes; *External: patient outcomes, patient experiences, patient access and adherence to medicines.	Develop the link between patient value and value for pharma based on the triple-aims of PHARMA industry: • Drive innovation in science; • Create patient value; • Generate financial ROI
Lowe et al., 2016	Empirical study	• As healthcare system continue to establish patients as the primary customer in the decision making, PHARMA needs to demonstrate medicine value relative to the outcomes experienced by patients; • The value of medicine is determined by the beneficiary – patients; • Structural, cultural, regulatory barriers are to be overcome.	Explore stakeholders' perspective on PE in the medicine development: • PHARMA perspective: lack of evidence to suggest that PE would deliver tangible benefits to justify the costs; A PE framework is needed; • Patients' perspective: patients can provide experiential knowledge of living with a disease, insights regarding benefits and risks assessment, and overall impact on daily life.
Smith et al., 2016	Scholarly article	• Patients are the beneficiary of the medical treatment and also bears their possible risks; patients' value is at the heart of the decision making; • PE needs to become integrated into the medicine development life cycle; • Collaboration of all stakeholders is necessary to implement PE.	Explore the role of PE in the assessment of benefits & risks of medicine along the development life cycle: • Patients view themselves as valued partner with increased health literacy in R&D; • PHARMA needs to balance patients' value and ROI, and find meaningful PE, overcome inherent conflicts concerning stakeholders' disparate goals; • Regulators need to resolve methodological, legal and ethical concerns relating to PE.
Blasimme et al., 2016	Scholarly article	• Patients can provide enormous information asset which needs to be harvested as a partnership; bio-banking promotes a shift in focus from individual to a particular group; • Bioethics need to consider patients' autonomy, moral pluralism, reciprocity, mutuality, solidarity, transparency and accountability, to maintain the public trust.	Debate bioethics concerning PE in precision medicine research and development of large-scale bio-banking beyond individual interests and moral: • PE is necessary to harvest enormous information repository for genetics-based precision medicine research; • Bioethics standards are to be defined to safeguard autonomy of participating patients.
Yeoman et al., 2016	Empirical study	• Provide information, education and support to enable PE; • Co-creation with patients through the medicine development processes; • Facilitate patients' access to medicine; • Value-based approach and transparency.	Develop a PE understanding from the patients' perspective: • Putting the patient first in an open and sustained engagement of the patient to respectfully and compassionately achieve the best experience and outcome for the person and their family.
Sacristan et al., 2016	Scholarly article	• Level of information provided to society and patients as a whole on research objectives and processes are to be improved;	Identify key areas for PE in medicine research and development: • Identify research priorities; • Design research;

		• Promote gradual emergence of expert patients in medical research.	• Improve access to clinical trials; • Oversee information to participants; • Assess patients' experiences; • Dissemination of research findings.
Hahn et al., 2017	Empirical study	Genuine PE are reflected in: • Genuine intent; • Relationship building; • Effective methods & structure in PE.	Explore how tokenism might influence engaging patients in research: • Tokenism is defined as the practice of making perfunctory or symbolic efforts to engage patients.
Crawford et al., 2017	Empirical study	• The more the researcher understands the need and value of patients, the more effective and efficient he can develop meaningful medicine for patients and improve healthcare.	Practical learnings from the patient-centred drug development (PCDD) initiatives: • Patients are valued co-researchers; • Patients perspective on value, benefits and risks are to be systematically captured by researchers; • Research becomes more transparent, convenient, and understood by patients.
du Plessis et al., 2017	Scholarly article	• Moving from medicine focus to patient value focus; • Benefits of PE includes identification of unmet patients need and the required product profile, optimize study design, shorten clinical trial time and reduce cost, improve patient adherence and outcome; • Patient access via strategic partnership with patient groups is a key enabler.	Address the questions of why, how, and what concerning the PE to the PHARMA: • The aim of PHARMA in medicine development is to serve patients living with a disease; • PHARMA needs to change mindset, build trust, learn, align and collaborate with patients; • PHARMA needs to shift focus from medicine to patient value, collaborate with patients, expert patients, and patient organizations.
Duffett, 2017	Empirical study	• PE has revolutionized the medical research with patients becoming active partners with physicians and researchers; • Increased time and effort, divergence from research agenda, non-equal roles, concerns about equality and representativeness, feasibility of study designs are potential barriers of PE.	Develop effective methods for PE in research: • Select the right patients to engage; • PE plan clearly defined; • Training and ongoing support of PE is provided; • Mutual respect and appreciate patients' experiential disease knowledge; • Start early, continue through, and evaluate outcomes.
Kirwan et al., 2017	Scholarly article	• Patient's experiential knowledge of living in a condition adds to the knowledge of research; • Initiate and maintain partnership; • Facilitate communication; • Capture, use, and optimize patients' perspective in research; • Ensure meaningful influence of PE; • Training for partnership; • Share and use joint learnings.	Develop guiding principles for effective PE in outcome research: • Establish supportive organizational policy; • Cultivate partnership via communication and shared goals; • Follow principles of respect, trust, reciprocity, and co-learning; • Address training need and facilitate knowledge transfer; • Allocate resources and ensure advanced planning; • Appreciate value of partnership.
Marzorati et al., 2017	Scholarly article	• Patients' value is the basics of healthcare system; • Patients' value includes positive outcomes, safety, satisfaction, accessibility and affordability.	Different value definition is the underlying driver for the paradigm shift in the healthcare system: • Re-emphasis of patients' value leads to the new healthcare system organized around the patients' need and emphasis of PE in the medicine development.

Mitchell et al., 2017	Scholarly article	• PE ensures development of medicines better aligned with patients' need; • Knowledgeable patients will contribute better to meaningful PE; • Difficulty in defining metrics to measure the return on investment (ROI) of PE.	Develop key components of PE in R&D context: • Understand patients; • Meet patients' need; • Connect patients; • Engage patients.
Richard et al., 2017	Theoretical research	• PE is conceptually confusing and would benefit from theoretical development; • Develop a shared vision and purpose; • Organize communication to foster knowledge translation; • Facilitate participatory research and maintain mutual benefits and interest.	Develop a relational PE model in clinical trials: • Relational ethical theories; • Participatory action research principles; • Systemic thinking; • Translational theories.
Boutin et al., 2017	Scholarly article	• A consistent understanding of what PE is, how and why is missing; • How to measure a successful PE for stakeholders is missing.	Identify priority areas to facilitate PE: • Facilitate cultural & process change; • Develop a global meta-framework for PE; • Develop information exchange platform; • Develop learnings and trainings.
Wilson et al., 2018	Scholarly article	• Level of engagement; • Nature of communication; • Stage of Clinical Outcome Assessment (COA).	Develop a PE methodology framework for COA: • Understand the disease or condition; • Conceptualize treatment benefit; • Develop outcome measures.
Pushparajah, 2018	Scholarly article	• Patient insights through PE creates value for healthcare; • Mutual understanding of PE is necessary for effective PE; • Standard PE methods and metrics are necessary to demonstrate the PE value.	Develop a Patient Group Engagement (PGE) model: • Shared ambition; • Transparency; • Accountability; • Respect.
Boudes et al., 2018	Empirical study	• PE in medicine development is suboptimal and needs improvement; • A structured systematic PE approach in medicine development is needed; • A practical PE model to connect stakeholders and demonstrate PE value is needed.	Develop a PE model in medicine development: • Meanings: what does PE mean? • Views: how important is PE? • Expectations: what are the PE goals to be achieved? • Next steps: what need to be done to achieve meaningful PE?
Bloom et al., 2018	Empirical study	• Establish partnerships with patient organizations (PO) with matching expertise; • Ensure PGE as essential partner in R&D, and not token voices; • Establish guiding principles to facilitate fit-for-purpose PGE.	Identify fundamentals of successful PGE: • Establish meaningful partnership; • Demonstrate mutual benefits; • Collaborate early on and often

Annex 2: Interview guide

Thank you for volunteering to participate in this interview. The aim of this interview is to gain your understandings and experiences concerning the patient engagement in the pharmaceutical medicine development context. The interview will take maximum 60 minutes and held in English. Feel free to ask for a break if you feel necessary. The interview will focus on your views and understandings to the questions; I will record the interview conversation as research data for the thesis development.

1. What do you think that "Patient Engagement in the medicine development context" mean from a value-creation perspective?
2. Do you have any experiences or observations regarding "patient engagement in medicine development"?
3. Can you identify examples of "patient engagement in medicine development"?
4. What do you think why should patients be engaged in medicine development with pharmaceutical company?
5. What do you think why should pharmaceutical company engage patients in medicine development?
6. What do you think are the values and benefits of "patient engagement in medicine development" for patients and healthcare?
7. What do you think are the key areas offering opportunities for patient engagement along the medicine development lifecycle, which might generate value for patients and healthcare?
8. What do you think needs to be in place for an effective "patient engagement in medicine development"?
9. What do you think are the facilitators and barriers to "patient engagement in medicine development"?
10. What do you think are the consequences and impacts of "patient engagement in medicine development"?
11. How would you define "patient engagement in the medicine development context" in one sentence from a value-creation perspective?
12. What do you think are the key components of "patient engagement in medicine development" from a value-creation perspective?
13. What do you think are the key operational principles that pharmaceutical companies need to follow, in order to incorporate patient engagement and generate values along medicine development lifecycle?

Do you have any other comments about the topic "patient engagement in the medicine development context"?

Annex 3: Recruitment strategy

Interview Participants (N≈30)	**Who should be contacted and where?**	**How to approach and proceed?**
Medicine development experts (N=11)	Search on leading pharmaceutical association websites: – European Federation of Pharmaceutical Industries and Associations (EFPIA) (https://www.efpia.eu/) – The Pharmaceutical Research and Manufacturers of America (PhRMA) (https://www.phrma.org/) Search from researcher's professional network to recruit medicine development experts working in pharmaceutical industry.	1. Interview candidates were searched according to selection criteria on these websites, blogs and social media; from professional network of the researcher; and from conferences and congresses; 2. Firstly, an *invitation email* (***Annex 4***) was sent out to potential participants asking for interest in participation; 3. After indicated participation interest, the *Participation Information Sheet* (***Annex 5***) together with the *Informed Consent Form* (***Annex 6***) were sent out to interested potential participant to gather written informed consent; 4. After receipt of written informed consent, researcher reached out to potential interview participant (per email or phone as indicated on the consent form) to schedule an interview. Face-to-face interviews conducting in a natural and safe environment were preferred; if distances not allow, a skype interview were organised, to catch meanings of both verbal and nonverbal languages. If all of the above was not possible, telephone interview was scheduled. 5. Interviews were conducted following *Interview Guide* (***Annex 2***) and audio-recorded. A summary of my final thesis would be shared with the participants if they wish.
Patients (or Services Users), patient advocates (N=10)	Post invitation and search on Patients' Blogs, Social Media, and Patient Groups: – PatientsLikeMe (https://www.patientslikeme.com/) – European Patients Forum (www.eu-patient.eu); – Patients as Partners Europe (www.theconferenceforum.org); – International Alliance of Patients' Organisation (IAPO) (https://www.iapo.org.uk/)	
PE experts (N=11)	Search on leading patient engagement initiatives' Blogs and Websites: – Patient Focused Drug Development Initiative: (https://www.fda.gov/about-fda/oncology-center-excellence/patient-focused-drug-development); – Patient Focused Medicines Development Initiatives: (http://patientfocusedmedicine.org/blog/); – European Patients' Academy Initiative: (https://www.eupati.eu/) – National Health Council Initiative: (https://nationalhealthcouncil.org/) Search from researcher's professional network to recruit PE experts, e.g., at PE conferences and congresses which researcher was attending.	

Annex 4: Invitation email

Dear xxx (name of the potential participant target),

I am a part-time research PhD student at the University of Gloucestershire, based in Germany.

Patient engagement has become a widely cited term in healthcare yet remains a poorly understood concept in relation to "what patient engagement is and how to achieve it" in the highly regulated medicine development context. My research aims to develop a consensus patient engagement concept, offer theoretical clarity to this concept, and derive guiding operational principles to inform practices.

I'm researching on patient engagement in the pharmaceutical medicine development context from a value creation perspective: how is the patient engagement concept defined and understood in the medicine development context; what are the theoretical underpinnings and core themes regarding the patient engagement concept; and what are the guiding operational principles for patient engagement in the medicine development context. To gather empirical data for this thesis, I conduct qualitative interviews with individuals having experiences, knowledge, and interest on this research topic.

I would like to invite you for an interview to explore your understandings and experiences related to this topic. Participation is voluntary and you will only be included if you provide your permission. I am working in the pharmaceutical industry as profession, but I will keep my influence minimal in this interview as independent inquirer and focus on capturing your understandings to the patient engagement topic.

The interview would last up to 60 minutes and would be held in English. Interview would be scheduled preferably face-to-face at a premise convenient to you, or via skype or telephone if distances do not allow. I would like to record the interview as it will be easier for me to listen to your responses without writing at the same time. No other person will have access to the record. I will use the information you give me as empirical data in my thesis. I will not mention your name, names that you mentioned and your organisation at any data analysis, written report, publications, and conferences. If you wish, I can send you a summary of my finished thesis for your information.

I look forward to hearing back from you. Thank you very much.

Xuemei Eichmann

Berlin, August 12, 2018

Contact Information:
Email:

Annex 5: Participant Information Sheet

Project Title	Exploring Patient Engagement in Pharmaceutical Medicine Development: A Value Creation Perspective
Researcher Contact	Xuemei Eichmann, MSc, MEng, MBA eMail:

Dear xxx (name of the potential participant who is indicating interest of participation),

Thank you for considering participation of an interview regarding patient engagement in medicine development. Patient engagement has become a widely cited term in healthcare yet remains a poorly understood concept in relation to "what patient engagement is and how to achieve it" in the highly regulated medicine development context. My research aims to develop a consensus patient engagement concept, offer theoretical clarity to this concept, and derive guiding operational principles. To gather empirical data for my thesis, I conduct qualitative interviews with individuals having experiences, knowledge, and interest on this research topic. I would like to interview you to explore your understandings and experiences concerning this topic. I am working in the pharmaceutical industry as profession, but I will take an outsider role in this interview as independent inquirer and focus on capturing your understandings to the patient engagement topic. Participation is voluntary and you will only be included if you provide your permission. You are free to withdraw from the study at any time prior to the publication without consequences.

The interview will last up to 60 minutes and will be held in English. Face-to-face interview at a premise convenient to you is preferred, or via skype or telephone if distances not allow. I would like to record the interview as it will be easier for me to listen to your responses without writing at the same time. No other person will have access to the record. I will use the information you give me as empirical data in my thesis. I will not mention your name, names that you mentioned and your organisation at any data analysis, written report, publications, and conferences. If you wish, I can send you a summary of my finished thesis for your information.

All your data will remain anonymous and be safely stored on a password protected computer, which can only be accessed to by the researcher. The data generated in the conversation will be treated as strictly confidential and used only for the purpose of this study. I will keep data for five years after the study finish. After five years, I will destroy the data. Please also refer to the Privacy Notice regarding measures taken by the researcher to protect your data privacy.

By taking part in this study, you may help researcher to advance this topic and add to the knowledge. There are no known risks associated with participation in this study. There are no commercial benefits will be offered for interview participation.

The University of Gloucestershire's Research Ethics Committee has approved this study. Please contact Dr Emily Ryall, Chair of the University of Gloucestershire's Research Ethics Committee, if you have any concerns. (Tel: 01242 , Email: k). Dr Ryall has no direct involvement in the study.

If you would like to participate in this study, please read and sign the informed consent form attached.

Thank you very much.

Xuemei Eichmann
Berlin, August 12, 2018

Annex 6: Informed consent form

Project Title	**Exploring Patient Engagement in Pharmaceutical Medicine Development: A Value Creation Perspective**
Researcher Contact	Xuemei Eichmann, MSc, MEng, MBA eMail: xuemeieichmannphd@gmail.com

Do you understand that I have asked you to participate in a research study?	Yes	No
Have you read and received a copy of the attached Participant Information letter?	Yes	No
Have you read and received a copy of the Privacy Notice for research participants?	Yes	No
Do you understand the benefits and risks involved in taking part in this research study?	Yes	No
Do you understand that you are free to contact the researcher to take the opportunity to ask questions and discuss this study?	Yes	No
Do you understand that you are free to refuse participation, or to withdraw from the study at any time prior to the publication without any consequence, and that your information will be withdrawn at your request?	Yes	No
Do you understand who will have access to your information?	Yes	No
Do you understand that I will keep your data confidential?	Yes	No

I wish to take part in this study:

Printed Name: _____

Signature: _____

Date: _____

Preferred Contact number: _____

Email: _____

Researcher Signature _____

Two Copies: One to be retained by participant.

Annex 7: Research ethics approval

UNIVERSITY OF GLOUCESTERSHIRE

Dr Emily Ryall
Research Ethics Committee Chair
Reader in Applied Philosophy

Oxstalls Campus, Longlevens,
Gloucester, GL2 9HW

Tel: +44 (0)1242
Email:

Xuemei Eichmann
via email

Thursday 22 November 2018

Dear Xuemei

Thank you for your application for ethical approval.

I am pleased to confirm ethical clearance for your research following ethical review by the University of Gloucestershire – Research Ethics Committee (REC).

Please keep a record of this letter as a confirmation of your ethical approval.

Project Title: Exploring Patient Engagement in Pharmaceutical Medicine Development: A Value Creation Perspective

Start Date: Monday 3 December 2018

Project Completion Date: Thursday 31 December 2020

REC Approval Code: REC.18.119.1

If you have any questions about ethical clearance please feel free to contact me. Please use your REC Approval Code in any future correspondence regarding this study.

Good luck with your research project.

Regards,

Dr Emily Ryall
Chair of Research Ethics Committee

Annex 8: Coding book developed from the theoretical phase

Themes derived from categories	Categories derived from codes	Codes from thematic analysis of literature data	Description of codes	Sources/ References
Patient Centricity *(Antecedent)*	Value-based Medicine *(Society Level)*	Driven by Patient Value	Patients are experts in their own disease and living with a condition, who can provide valuable insights in assessment of meaningful benefits, risks, and acceptance in relation to medicine development.	34/61
		Driven by Innovation & Sustainability	Healthcare issues in balancing innovation, benefits, costs, and sustainability is a key driver to pursue a paradigm shift to VBM, which is supposed to resolve these healthcare issues.	17/25
		Driven by paradigm shift to VBM	Healthcare is shifting towards a VBM paradigm with patient value at the core of all stakeholders, which proposes that healthcare value should be measured around the health outcome achieved around patient.	68/158
	Patient as Consumer & Expert *(Patient Level)*	Patient as Consumer & Expert	Overarching ethical argument that patient as consumers having the right for PE; and patients have unique experiential knowledge as expert, whose inputs need to be captured in medicine development.	21/25
		Patients' rights and ethics	A manifestation of the democratization of medicine development referring to patients' rights of participation of activities that impact on their life, such as in the context of medicine development.	12/18
		Health literacy & capacity	Patients' cognitive capability in participation of PE through expression of experiences, preferences, giving meaningful inputs and assessment in the context of medicine development.	50/90
	Patient Centricity *(PHARMA Level)*	Patient-centric culture	Adopting a patient-centric culture and strategy at PHARMA was deemed as a prerequisite for a meaningful PE in medicine development.	41/63
		PE guidance & incentives	A clear guidance and incentives associated with PE given by regulators and HTA agents was considered as a key prerequisite for PHARMA's move into meaningful PE in medicine development.	21/33
		Recognize the value of PE	Recognizing the genuine value of PE was suggested as the prerequisite for PHARMA to embrace PE instead of taking only tokenism effort.	20/48
Co-Creation *(Attribute)*	Partnership & Collaboration *(Society Level)*	Shared Leadership	Active engagement of patients with HCPs in joint clinical decision and policy makings was considered as key attribute foo PE.	30/39
		Patient as Value Co-Creator	Interactions between patients and HCPs allow integration of patients' experiences, resources into the healthcare activities and maximize the health outcome, which was deemed as a key attribute to PE.	23/54
		Partnership & Collaboration	Partnership & collaboration was considered as the foundation for PE following principles of reciprocal, respect, trust, co-learning, equality, and transparency.	52/92
	Patient as Value Co-Creator *(Patient Level)*	The Engaged Patient	Engaged patient was described as active, literate, self-aware, self-efficacious, and having power to advocate and abilities to interact with healthcare system and HCPs.	55/144
		Patient as Value Co-Creator	Patients' experiential knowledge is an asset and resources, which should be brought into the medicine development as co-creator via PE.	55/91
		Presence of Patients' Voices	Patients' physiological, physical, psychological, and social needs should serve as focal point in the overall design of medicine.	9/9
	Integration of patient value *(PHARMA Level)*	Integration of Patient Value	Patients' inputs need to be incorporated into the design, development, assessment, review, and approval of medicine through PE.	40/61
		Patient as Value Co-Creator	A means of interactions with patients to incorporate patient value into the medicine development processes – a key attribute for PE.	82/200
		Partnership & Collaboration	A means of interactions to generate mutual benefits based on principles of systematic, reciprocal, trustful, ethical, and mutual value-adding, was indicated as a key attribute to PE in medicine development.	15/29
Improved Value *(Consequence)*	Improved Healthcare Value *(Society Level)*	Improved Healthcare Value	Improved healthcare outcomes, performance, and quality was suggested as a consequence of PE in the context of medicine development.	39/64
		Improved Patient Experiences	Improved patient experiences and satisfaction as a consequence of PE through shared ambition, transparency, accountability and respect.	19/24
		Improved Healthcare Sustainability	PE was supposed to contribute to improved service quality, outcomes, and efficiency, thus improve the healthcare sustainability as a consequence of PE at the society level.	17/25

	Improved Patient Value *(Patient Level)*	Improved adherence & compliance	PE was supposed to contribute to improved patients' adherence to the treatment and thus better outcomes, which is associated with the positive cognitive and behavioural changes of an engaged patient.	24/38
		Improved relevance & adoption	PE was supposed to contribute to improved relevance and adoption of the medical solutions, which is associated with perceived shared decision power, and the feeling of self-responsibility.	8/10
		Improved patient experience & trust	PE was supposed to contribute positively to the patients' journey in terms of healthy behaviour, positive experiences, increased confidence, trust, and commitment, as a consequence of PE at a patient level.	13/16
	Improved Business Value *(PHARMA Level)*	Improved Patient Value & Health Outcomes	PE was supposed to deliver benefits for patients, society and PHARMA in terms of better health outcomes, co-learnings, co-creation and dissemination of research results and knowledge, as a consequence.	37/78
		Improved Innovation & Business Success	PE was supposed to help PHARMA better understand patients' need, develop innovative solution to address these needs and achieve ROI, as a consequence of PE at the PHARMA level.	30/56
		Improved Reputation & Trust	PE was supposed to help PHARMA to improve the partnership with patients and establish transparency, credibility, and regain reputation and trust as a consequence of PE at the PHARMA level.	24/33
Themes derived from Categories	**Categories derived from Codes**	**Codes from thematic analysis of literature data**	**Description of codes**	**Sources/ References**
Discrepancy of VALUE perspectives & PE Methodology challenges along the medicine development *(Barrier)*	Discrepancy of VALUE perspectives of healthcare stakeholders *(Society Level)*	Discrepancy of VALUE perspectives	Different VALUE perspectives are pursued by healthcare stakeholders (i.e., regulators, HTA agents, HCPs, PHARMA, and patients); lacking aligned VALUE along the medicine development was considered as a barrier to PE at the society level.	27/37
		Cultural resistance	HCP's power imbalance and resistance to lay involvement, the high methodological hurdles, were suggested as major cultural barriers to the PE at the society level.	21/28
		ESL constraints	ESL issues concerning data privacy and conflict of interests were identified as major barrier for HCPs to adopt the PE approach in the context of medicine development at the society level.	18/23
		Lack of incentives and evidence of PE benefits	Little evidence is available demonstrating the assumed effectiveness and beneficial outcomes associated with the concept of PE, was considered as a barrier to PE at the society level.	36/70
	Methodology challenges to integrate PE into established medicine development *(PHARMA Level)*	Cultural resistance & Tokenism	PHARMA was considered as reluctant to go beyond lip services without genuine interest and real effort for PE, which was suggested as a barrier to PE at the PHARMA level in medicine development.	32/56
		How-Methodology challenges	Methodological challenges to incorporate heterogeneous patients' inputs into the well-established scientific methods regulated by health authorities and HTA agents, was indicated as a major barrier to PE.	27/51
		ESL constraints	The perceived compliance risk associated with PE within an insufficient ESL framework was suggested as a key barrier for PHARMA in PE.	13/21
		Lack of evidence of PE benefits	A lack of financial evidence associated with the PE activities was indicated as a major barrier for PHARMA to take a PE approach.	32/57
	Methodology challenges to engage the right patients with the right inputs *(Patient Level)*	Health literacy & capacity	The scepticism that patients as lay users can contribute to the medicine development without appropriate medical training was indicated as a barrier to PE at the patient level in medicine development.	14/28
		How-the right patients & right patient inputs	The generalizability of individual and diverse patients' voices, and the multiplicity of patients' roles and potential biases, was suggested as a methodological barrier to PE in the context of medicine development.	12/38
		Organization & compensation	Logistic challenges, inadequate compensation, and costly PE endeavours in terms of time and resources was considered as a key barrier to PE.	11/11
Development of a PE methodology and Process Framework based on aligned VALUE along the medicine development. *(Facilitator)*	Development of PE Conceptual Framework with aligned VALUE *(Society Level)*	PE Framework & platform based on aligned VALUE	Develop a meta-PE framework based on aligned VALUE endorsed by all healthcare stakeholders was suggested to positively advance the adoption of PE in the context of medicine development.	19/31
		Define ESL framework for PE	Develop a sufficient ESL framework to guide the PE activities was considered to facilitate the adoption of PE in the practices.	8/17
		Incentives for PE – align reimbursement with patient value	Create incentives through regulation and reimbursement policy for PE activities in medicine development was suggested to advance the PE as a facilitator in the context of medicine development.	8/11

		Create evidence base for PE	Create evidence base to demonstrate effectiveness and benefits of PE in the context of medicine development was assumed as a facilitator to PE in the context of medicine development.	5/7
	Development of aligned PE process framework endorsed by all healthcare stakeholders ***(PHARMA Level)***	Culture change & Process Design	PHARMA's cultural changes and genuine willingness to integrate PE into the existing medicine development processes of PHARMA was suggested as a facilitator to PE in the context of medicine development.	25/41
		Aligned PE Framework endorsed by all HC stakeholders	Define an aligned PE conceptual model endorsed by all healthcare stakeholders was considered as an important facilitator to advance PE in the context of medicine development.	26/36
		Define PE measurements & generate evidence of PE benefits	Define PE measurement metrics and generate evidence base for the assumed positive outcomes associated with PE in the context of medicine development, was argued as a key facilitator for the PE advancement.	21/26
	Development of aligned methodology to incorporate meaningful patients' inputs. ***(Patient Level)***	Provide education & training to support patient experts in PE	Provide educations, trainings, and support to patients to improve their health literacy and capability was considered as a facilitator to PE in the context of medicine development at a patient level.	18/21
		Define PE methodology of incorporating patients' inputs	Development of methodology to incorporate diverse and representative patients' inputs and integrate these data into the scientific package of medicine development was considered as a facilitator for PE advancement in medicine development at a patient level.	15/17
		Enhance PE through collaboration with Patient Organizations	Collaboration with patient organizations – an important intermediary to the patients' network was suggested to facilitate the PE in the context of medicine development at a patient level.	12/17

Annex 9: Coding book developed from the fieldwork phase

Themes derived from Categories	Categories derived from Codes	Codes from thematic analysis of Interview Data	Description of codes	Sources/ References
The presence of patients' voices in medicine development in the shift to a VBM paradigm *(Antecedent)*	Regulators & HTA ask for presence of patients' voices in medicine development *(Society Level)*	Personalized medicine and focus on Patient Value	Patients are consumers, healthcare and medicine should build on patient value through understanding and meeting individual patient's needs.	13/19
		Healthcare value focuses on innovation and sustainability	Regulators and HTA agents appreciate the presence of patients' perspectives in decision-makings to balance innovation with sustainability	24/47
		Paradigm shift to VBM in healthcare system	Healthcare is moving towards a value-based rewarding system; and value is defined as positive outcomes for patients.	11/17
	Patient as Consumer & Expert wants patients' voices to be heard. *(Patient Level)*	Patients as Consumers & Experts want their voices being heard	Patients are both consumers and experts of healthcare and medicines, who want their voices being heard and contribute to a positive outcome.	19/41
		Moral imperative of patients' rights and ethics to be engaged	It is a moral imperative to engage patients in healthcare and medicine because they bear the impact of the treatment -- it's the right thing to do.	8/13
		Patients' health literacy and capacity in increasing	Patients' health literacy and capacity to collaborate are increasing significantly due to the democratization of information and the emergence of patient organizations.	15/38
	PHARMA to adopt patient-centricity - understand patients' needs & perspectives *(PHARMA Level)*	Patient centric culture	Patient centricity is the right thing to do and the future, so PHARMA need to consider providing tailor-made solution and 'beyond the pull' services to meet the needs of individual patient.	20/32
		PE guidance and incentives	Regulatory requirements on PE serves as powerful opponents and incentives for PHARMA to take on the PE approach in medicine development	16/30
		Appreciate patients' inputs and participation	PHARMA's intrinsic motivation to improve patients' outcomes is suggested as the most impactful precedent for PHARMA to appreciate patients' inputs and participation in medicine development.	18/32
Co-Creation through combining knowledge and experiences of *PHARMA* and patients in interaction *(Attribute)*	Patients as partner in medicine review and approval processes of regulators *(Society Level)*	Shared Leadership & decision-making by regulators	Shared leadership and decision-making with participation of patients were suggested as key attribute of PE at the society level, which is reflected in the PE requirements of health authorities and HTA agents in medicine review, approval, and reimbursement decisions.	8/9
		Value Co-creation through PE	Getting patients' perspectives involved at every stage of medicine development lifecycle and include these data into the benefit-risk assessment and decision making around medicine development was indicated as a key VCC component associated with PE	6/10
		Partnership & collaboration of all healthcare stakeholders	Partnership and collaboration were considered as a key principle attribute associated with PE, which are based on mutual respects and benefits, transparency, trust, and co-learnings.	3/4
	Patient as value co-creator – leverage patients' experiences in living with disease as an asset *(Patient Level)*	Engaged patients	Educated and engaged patients are the key attribute on the patient level through PE in the medicine development by consideration of patients' experience which serves as an asset to improve outcomes.	6/7
		Patient as Value Co-Creator	Patients contribute to the medicine development as research partners, advisors, and co-producers of evidence.	15/25
		Patients' voices are heard, and needs are understood	A key attributed associated with PE in medicine development at the patient level was evidenced that patients' inputs are integrated in the medicine development processes through PE	7/12
	Presence of patients' voices in medicine development *(PHARMA Level)*	Presence of patient value in medicine development	A key attribute of PE in medicine development at PHARMA level was indicated as the presence of patient value and perspectives at each stage of the medicine development lifecycle.	27/126
		Value Co-Creation in medicine development	VCC is a key attribute of PE in medicine development through consultation – capturing patients' inputs, and collaboration – joint oversight and decision-making with patients along the medicine development lifecycle.	21/43
		Partnership and Collaboration	Key process attribute of PE in medicine development was suggested as partnership and collaboration, which are built on trust, transparency, respect and commitment between PHARMA and patients.	26/83

Improved Value for patients and all healthcare stakeholders ***(Consequence)***	Improved Healthcare Value for Society ***(Society Level)***	Improved Healthcare Value	PE was supposed to improve the relevance of research, close the gaps, and set research priority from a public health aspect, to have the right drug to the right patient with the right dose at the right time, thus improve the healthcare.	4/4
		Improved Patient Value	PE was suggested to improve the patients' experiences and health outcomes through better communication and understandings between patients and clinical teams in medicine development, thus improve the patient value.	2/4
		Improved Innovation & sustainability	PE was expected to deliver improved quality, efficiency, innovation, and sustainability through developing better medicines to meet unmet medical needs, thus resolving the healthcare issues in sustainability and innovation.	6/8
	Improved Patient Value for patients ***(Patient Level)***	Improved patient value and health outcomes	PE in medicine development was supposed to improve the efficacy, compliance, and patients' experiences, thus improve the patient value and health outcomes.	6/8
		Improved relevance and adoption	PE in medicine development was assumed to improve the relevance and thus increased adoption of the medicine by patients through in-depth consideration of patients' need both on individual and population level.	3/4
		Improved patient experience and trust	PE in medicine development was expected to deliver the right drug to the right patient with the right dose at the right time, thus enhance patients' experience and trust between PHARMA and patients.	5/5
	Improved Business Value for PHARMA ***(PHARMA Level)***	Improved patient value and health outcomes	PE in medicine development was suggested to deliver better medicines that meet patients' needs and thus, contributing to improved patient value and healthcare outcomes at the PHARMA level.	11/22
		Improved Innovation & Business success	PE in medicine development was evidenced to improve the clinical trial data quality, mitigate risks through matching product profiles with patients' needs, which contribute to both operational outcomes and support regulatory approvals, thus improve innovation and business success of PHARMA.	16/41
		Improved reputation and trust	PE in medicine development was supposed to help PHARMA in trust-building with patients, demonstrating themselves as honest, transparent, and trustworthy partner, thus improving the reputation and trust in the long term and in a sustainable way.	10/13
Value discrepancy, challenges in methodology, process and culture ***(Barrier)***	HCP's paternalism & missing of aligned PE Framework including methodology and processes. ***(Society Level)***	HCP's paternalism & cultural resistance	HCP's paternalism and cultural resistance was suggested a key hurdle to the concept of PE in medicine development.	7/9
		Regulatory constraints, lack of ESL and social framework	Regulatory constraints regarding insufficient ESL and social framework, perceived compliance risks surrounding the PE in medicine development was considered as a key hurdle to the uptake of PE in medicine development.	13/25
		How – methodology and process challenges	Methodology and process challenged related to PE in medicine development, e.g., healthcare systems are not built around patients, terminology issues with fussy definitions, increased complexity associated with PE, etc., was claimed as a key hurdle to PE.	17/21
	Patients' health literacy, capacity & maturity of PO ***(Patient Level)***	Health literacy and capacity of patients; maturity of patient organization	Patients' health literacy and capability in cooperation with clinical teams in the medicine development was suggested as a hurdle at the patient level, which is also depending on the maturity of patient organization that should help to build up the patient research network and close the gap.	9/13
		How – the right patients with the right inputs	The methodology issue regarding how to get access to the right patients and capture the right inputs, and further integrate these patients' data into the existing data collection processes in medicine development was considered as a hurdle at the patient level.	4/5
		Power imbalance and wishful thinking	Power imbalance of medical doctors and HCPs over patients was still considered as a hurdle of PE in terms of language barriers, patients' inputs were perceived as wishful thinking instead of expression of needs.	5/6
	PHARMA's culture resistance & Tokenism and disconnect with patients ***(PHARMA Level)***	Culture resistance & Tokenism	PHARMA was considered disconnected with patients, science-driven instead of patient-centric, fear of loose control, not inclusive and ready for partnership, seeing PE as additional burden, not appreciating the value of PE, thus cultural resistance and tokenism of PHARMA was suggest as a key hurdle to PE in medicine development.	27/89
		How-Methodology & process challenges	Methodology and process issues regarding lacking common understandings about the meanings of PE, perceived legal constraints and compliance risks, complexity in serving multiple-stakeholders with divergent expectations was evidenced as a big hurdle to PE in the context of medicine development.	19/41
		Lack of evidence and incentives of PE outcomes and benefits	Lack of evidence concerning the assumed positive outcomes related to PE and therefore the lack of incentives regarding PE in medicine development was suggested as a key hurdle to PE at the PHARMA level	16/23

Develop aligned PE framework with multi-stakeholders along medicine development lifecycle ***(Facilitator)***	Develop aligned PE methodology & Process Framework. ***(Society Level)***	Incentives and drive cultural changes	PE-related regulatory requirements were considered as impactful incentives which will drive PHARMA to adopt PE approach, and overcome cultural resistance at the PHARMA level	13/18
		Develop PE framework with aligned value, methodology & process	Develop a master PE framework based on aligned value, methodology and processes was suggested as a big facilitator to the concept of PE in the context of medicine development.	7/8
		Generate evidence for PE benefits	PE was suggested as a complex phenomenon within a multi-dimensional ecosystem which needs to be performed right in order to deliver the assumed benefits; generating evidence of the PE outcomes was deemed as a facilitator to enhance the acceptance of PE.	5/7
	Engage the right patients with the right purpose. ***(Patient Level)***	Improved capacity and qualification of patients as research partners	Patients with adequate trainings and qualifications as research partners with however independent, unbiased, authentic voices to generate representative voices with rigorous methods was suggested as a key facilitator to the concept of PE in the context of medicine development.	10/21
		Methodology: Engage the right patients for the right purpose	Define methodology to engage the right patients for the right purposes was indicated as a key facilitator to the concept of PE in the context of medicine development.	5/6
		Collaboration with patient Organization	Collaborate with patient organizations who are increasingly representing patient community in interactions with PHARMA was evidenced as a key facilitator to PE in medicine development.	8/11
	Establish processes to integrate patients' voices in medicine development ***(PHARMA Level)***	Culture change & process design	Establishing trusted leadership to drive inclusive culture, mindset, and philosophical changes, enhance transparency and repair reputation, was suggested as a key facilitator of PE at the PHARMA level.	18/26
		Define PE framework endorsed by stakeholders	Develop an aligned PE framework covering definitions, methodology and processes endorsed by relevant stakeholders was indicated as a key facilitator to the concept of PE in the context of medicine development.	11/19
		Define PE measurement metrics and generate evidence of PE benefits	Develop measurement metrics linking PE activities with business success of PHARMA to generate evidence demonstrating value associated with PE was considered a key facilitator to the concept of PE in the context of medicine development.	10/17

Annex 10: Thematic Map developed from the final analytical phase

Final Core Themes	Categories from Theoretical Phase	Codes from Theoretical Phase	Categories from Fieldwork Phase	Codes from Fieldwork Phase
Patient Centricity *(Antecedent)*	Value-based Medicine *(Society Level)*	Driven by Patient Value	The presence of patients' voices in medicine development in a shift to VBM *(Society Level)*	Personalized medicine and focus on Patient Value
		Driven by Innovation & Sustainability		Healthcare value focuses on innovation and sustainability
		Driven by paradigm shift to VBM		Paradigm shift to VBM in healthcare system
	Patient as Consumer & Expert *(Patient Level)*	Patient as Consumer & Expert	Patient as Consumer & Expert wants patients' voices to be heard. *(Patient Level)*	Patients as Consumers & Experts want their voices being heard
		Patients' rights and ethics		Moral imperative of patients' rights and ethics to be engaged
		Health literacy & capacity		Patients' health literacy and capacity in increasing
	Patient Centricity *(PHARMA Level)*	Patient-centric culture	PHARMA to adopt Patient Centricity-understand patients' needs and perspectives *(PHARMA Level)*	Patient centric culture
		PE guidance & incentives		PE guidance and incentives
		Recognize the value of PE		Appreciate patients' inputs and participation
Co-Creation *(Attribute)*	Partnership & Collaboration *(Society Level)*	Shared Leadership	Patients as partner in medicine review and approval processes of regulators *(Society Level)*	Shared Leadership & decision-making by regulators
		Value Co-Creation		Value Co-creation through PE
		Partnership & Collaboration		Partnership & collaboration of all healthcare stakeholders
	Patient as Value Co-Creator *(Patient Level)*	The Engaged Patient	Patients as value co-creator: Leverage patients' experiences in living with disease as an asset *(Patient Level)*	The Engaged patients
		Patient as Value Co-Creator		Patient as Value Co-Creator
		Patients' needs are addressed		Patients' voices are heard, and needs are understood
	Integration of Patient Value *(PHARMA Level)*	Presence of Patient Value	Co-creation through combining knowledge and experiences of PHARMA and patients in interaction *(PHARMA Level)*	Presence of patient value in medicine development
		Value Co-Creation		Value Co-Creation in medicine development
		Partnership & Collaboration		Partnership and Collaboration
Improved Value *(Consequence)*	Improved Healthcare Value *(Society Level)*	Improved Healthcare Value	Improved Healthcare Value *(Society Level)*	Improved Healthcare Value
		Improved Patient Experiences		Improved Patient Value
		Improved Healthcare Sustainability		Improved Innovation & sustainability
	Improved Patient Value *(Patient Level)*	Improved adherence & compliance	Improved Patient Value *(Patient Level)*	Improved patient value and health outcomes
		Improved relevance & adoption		Improved relevance and adoption
		Improved patient experience & trust		Improved patient experience and trust

	Improved Business Value ***(PHARMA Level)***	Improved Patient Value & Health Outcomes	Improved Business Value ***(PHARMA Level)***	Improved patient value and health outcomes
		Improved Innovation & Business Success		Improved Innovation & Business success
		Improved Reputation & Trust		Improved reputation and trust
Challenges in Value, Process, & Methodology ***(Barrier)***	Discrepancy of VALUE perspectives ***(Society Level)***	Different VALUE perspectives	HCP's paternalism and missing aligned PE framework including methodology and processes. ***(Society Level)***	HCP's paternalism & cultural resistance
		Cultural resistance		Regulatory constraints, lack of ESL and social framework
		ESL Framework		How – methodology and process challenges
		Lack of incentives and evidence of PE benefits		
	How – the right patients with the right inputs ***(Patient Level)***	Health literacy & capacity	Patients' health literacy, capacity, and maturity of patient organization ***(Patient Level)***	Health literacy and capacity of patients; maturity of patient organization
		How to incorporate the inputs from the right patients		How – the right patients with the right inputs
		Organization & compensation		Power imbalance and wishful thinking
	How-methodology & process challenges (***PHARMA Level)***	Cultural resistance & Tokenism	PHARMA's culture resistance, tokenism, mistrust, disconnect with patients ***(PHARMA Level)***	Culture resistance & Tokenism
		How – Methodology challenges		How-Methodology & process challenges
		ESL framework		Lack of evidence and incentives of PE outcomes and benefits
		Lack of evidence of ROI of PE		
Develop PE framework with aligned Value & Methodology ***(Facilitator)***	PE Framework based on aligned VALUE perspectives ***(Society Level)***	PE Framework with aligned VALUE	Develop multi-stakeholder aligned PE methodology and process framework. ***(Society Level)***	Incentives and drive cultural changes
		Define ESL Framework		Develop PE framework with aligned value, methodology & process
		Incentives for PE		Generate evidence for PE benefits
		Create evidence of PE benefits		
	Define methodology incorporating patients' inputs. ***(Patient Level)***	Culture change & process design	Engagement with the right patients with the right purpose ***(Patient Level)***	Improved capacity and qualification of patients as research partners
		Aligned PE Framework with stakeholders		Methodology: Engage the right patients for the right purpose
		Define PE measurements & evidence generation of PE outcomes		Collaboration with patient Organization
	Define methodology & process for PE. (***PHARMA Level)***	Education & Trainings to support Patient Experts in PE	PHARMA to establish processes and methodology including patients' voices in medicine development. ***(PHARMA Level)***	Culture change & process design
		Define Methodology to incorporate patients' inputs		Define PE framework endorsed by stakeholders
		Lack of evidence of ROI of PE		Define PE measurement metrics and generate evidence of PE benefits

Annex 11: University Author Consent Form for a Research Thesis

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at Cheltenham and Gloucester

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Author's Name: XUEMEI EICHMANN

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EXPLORING PATIENT ENGAGEMENT IN PHARMACEUTICAL MEDICINE DEVELOPMENT: A VALUE CREATION PERSPECTIVE

Degree: PHD

School: SCHOOL OF HEALTH & SOCIAL CARE

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