D2.1 short report of existing patient engagement practices and processes

777450 - PARADIGM

Patients Active in Research and Dialogues

for an Improved Generation of Medicines

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[1] Use one of the following codes:
R: Document, report (excluding the periodic and final reports)
DEM: Demonstrator, pilot, prototype, plan designs
DEC: Websites, patents filing, press & media actions, videos, etc.
OTHER: Software, technical diagram, etc.
[1] Please choose the appropriate reference and delete the rest:
PU = Public, fully open, e.g. web;
CO = Confidential, restricted under conditions set out in Model Grant Agreement;
CI = Classified, information as referred to in Commission Decision 2001/844/EC.

Definitions

Partners of the PARADIGM Consortium are referred to herein according to the following codes:

- **EPF**. EUROPEAN PATIENTS FORUM (Luxembourg) – **Project Coordinator**
- **EURORDIS**. EUROPEAN ORGANISATION FOR RARE DISEASES ASSOCIATION (France)
- **EATG**. EUROPEAN AIDS TREATMENT GROUP (Germany)
- **AE**. ALZHEIMER EUROPE (Luxembourg)
- **AIFA**. AGENZIA ITALIANA DEL FARMACO (Italy)
- **HTAi**. HEALTH TECHNOLOGY ASSESSMENT INTERNATIONAL (Canada)
- **IACS**. INSTITUTO ARAGONES DE CIENCIAS DE LA SALUD (Spain)
- **FSJD**. FUNDACIO SANT JOAN DE DEU (Spain)
- **VU-ATHENA**. STICHTING VU (The Netherlands)
- **UOXF-CASMI**. THE CHANCELLOR, MASTERS AND SCHOLARS OF THE UNIVERSITY OF OXFORD (United Kingdom)
- **EFGCP**. EUROPEAN FORUM FOR GOOD CLINICAL PRACTICE (Belgium)
- **SYNERGIST**. THE SYNERGIST (Belgium)
- **SYNAPSE**. SYNAPSE RESEARCH MANAGEMENT PARTNERS SL (Spain)
- **EFPIA**. EUROPEAN FEDERATION OF PHARMACEUTICAL INDUSTRIES AND ASSOCIATIONS (Belgium) - **Project Leader**
- **MSD Corp.** MERCK SHARP & DOHME CORP (United States)
- **UCB**. UCB BIOPHARMA SPRL (Belgium)
- **ABPI**. THE ASSOCIATION OF THE BRITISH PHARMACEUTICAL INDUSTRY (United Kingdom)
- **AMGEN**. AMGEN LIMITED (United Kingdom)
- **BAYER**. BAYER AKTIENGESELLSCHAFT (Germany)
- **GSK**. GLAXOSMITHKLINE RESEARCH AND DEVELOPMENT (United Kingdom)
- **GRT**. GRUENENTHAL GMBH (Germany)
- **JANSSEN**. JANSSEN PHARMACEUTICA NV (Belgium)
- **LILLY**. Eli Lilly and Company Limited (United Kingdom)
- **LUNDBECK**. H. LUNDBECK AS (Denmark)
- **MERCK**. MERCK KOMMANDITGESELLSCHAFT AUF AKTIEN (Germany)
- **NOVO NORDISK**. NOVO NORDISK A/S (Denmark)
- **PFIZER**. PFIZER LIMITED (United Kingdom)
- **ROCHE**. F. HOFFMANN-LA ROCHE AG (Switzerland)
- **SERVIER**. INSTITUT DE RECHERCHES INTERNATIONALES SERVIER (France)
- **VFA**. VERBAND FORSCHENDER ARZNEIMITTELHERSTELLER EV (Germany)
- **SARD**. SANOFI-AVENTIS RECHERCHE & DEVELOPPEMENT (France)
- **NOVARTIS**. NOVARTIS PHARMA AG (Switzerland)
- **COVANCE**. COVANCE LABORATORIES LTD (United Kingdom)
- **ALEXION**. ALEXION SERVICES EUROPE (Belgium)

- **Consortium.** The PARADIGM Consortium, comprising the above-mentioned legal entities
- **Consortium Agreement**. Agreement concluded amongst PARADIGM participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

Abbreviations

PFMD	Patient Focused Medicines Development	PILG	Paradigm International Liasion Group
PCORI	Patient-Centered Outcomes Research Institute	PE	Patient Engagement
CTTI	Clinical Trials Transformative Initaittive	CER	Comparative Effectiveness Research
EUPATI	European Patients Academy	PRO	Patient reported outcomes
HTA	Health Technology Assessment Bodies	EMA	European Medicines Agency
PFDD	Patient Focused Drug Development	FDA	Food and Drugs Agency
EATG	European Aids treatment group	HTAi	HTA international
AE	Altzehimer Europe	NICE, UK	National Institute for Health and care excellence
EFPIA	European Federation of Pharmaceutical Industries and Associations	PPI	Patient and Public Involvement
WP2	Work package 2	R&D	Research and development
SOP	Standard operating procedure		

1. Executive Summary

The overarching mission of the PARADIGM consortium is to provide a framework that allows structured, meaningful, sustainable and ethical patient engagement (PE) throughout three key decision-making points of the development of medicinal products: Research priority setting, Design of clinical trials and, Early dialogues with regulators and health technology assessment (HTA) bodies.

Drawing upon key PE initiatives consolidated from consortium partners, the overall aim of work package 2 (WP2) is to undertake a gap analysis (i.e. the comparison of actual performance with potential or desired performance) in order to provide an inventory of gaps across existing PE practices (that include frameworks, guidance, guidelines) and processes (that include protocols, methods, tools or templates), along with case studies that are relevant to patient engagement initiatives. The desired performance that WP2 is measuring against will be largely based according to the stakeholder needs, expectations and preferences that have been identified from the literature, survey and focus groups, and three Delphi methodologies conducted (see appendix).

The purpose of this document is to provide an interim report which represents a high level overview of the analysis to date around existing PE practices and processes, combined with some of the already known gaps in PE based on anecdotal and experiential evidence, which will be integrated into the first iteration of the tool being developed for gap analysis. This interim information is not yet designed to be exhaustive or conclusive as to the status of PE in medicines development. Rather it represents a snapshot of PE in medicines development with a focus on the 3 decision making points addressed by the consortium. Further interrogation of the initiatives identified here will be undertaken during the next stages of work to identify in detail where gaps exist, why the gaps might exist, and what could be developed (e.g. new guidance, tools and methods) in order to enhance and sustain impactful patient engagement.

We define here the types of PE initiatives that we aim to include in a detailed analysis. Briefly, these form 3 levels of information in descending order of detail and applicability; Level 1 – Frameworks: guidance and guidelines, including those that may also contain additional tools embedded in them, Level 2: Processes – tools, standard operating procedures (SOP), methods, protocols and templates, and Level 3: Individual case studies that describe in part or wholly the PE activity start to finish. These levels were then applied to inclusion/exclusion criteria from an initially large list of PE initiatives identified from within the consortium. The criteria were; 1) Were patient(s) or patient groups directly engaged? 2) Is the PE activity part of a i) framework, guidance or guideline, ii) process, or iii) case study? and, 3) Does the framework/process/practice or case study cover 1 or more of the 3 decision-making points? To complement the descriptive analysis, a targeted sampling approach was also conducted to identify some of the key frameworks and guidance that originate from different stakeholder groups (industry, HCP, regulator, HTA and patient organisations) to identify common themes covered by all, and conversely help to indicate where some of the gaps may lie.

One hundred and sixty-five initiatives were subsequently identified that fulfilled our criteria for inclusion (see section 3.3). From this sample a majority covered the design of clinical trials (59%) with one fifth covering each of research priority setting (16%) and early dialogues with regulators and HTA (12%). Nearly three quarters (73%) covered the general adult population, with very few indicating that they included specialist populations, such as young people, people with dementia, or their carers (all ~5%). Of the published guidelines and defined processes (<30% of total) there are several good detailed examples that cover either, the entire medicine research and development (R&D) continuum and/or specific stakeholder groups. Some of the common themes addressed in guidance by different stakeholder were as follows; 1) Defining the objective of the planned interaction and/or areas of common interest (“shared purpose”), 2) Establishing/defining roles and responsibilities, 3) Ensuring transparency in all processes (publicly availability of who, what, when and finances), 4) Providing compensation for time/costs and help with logistical planning, 5) Building capacity and capability (for patient’s to be effective contributors and for stakeholders to engage effectively with patients), and 6)

Optimizing insight generation from patient experiences and knowledge of living with the disease.

Overall some guidance documents are supported with templates and tools and detailed methods to guide the implementation of the underlying principles – but many guidance documents lack this more holistic approach to implementation. Three quarters (76%) of initiatives are individual case studies that contain varying degrees of information on the process and outcomes of the PE activity. There is a general lack of published detail to those examples, with relatively few that specify the guidance, guidelines and tools used to carry out a PE activity, or the level to which patients were actually involved in a given PE activity.
At this stage some identified deficiencies (in guidance)[2] that emerged from the general PE landscape include the lack of direct link between guiding principles and the details of how to actually implement them, and the further logical link to additional tools and templates to support that implementation. Included in those gaps are the specifics on how to adapt guidelines to stakeholder needs, and in particular to vulnerable populations and specific decision-making points of research priority setting, and early dialogues.
In terms of processes, tools and templates, some additional gaps were identified where greater detail or applicability is needed that could in part or whole account for vulnerable populations, or EU member state structures and legal systems. These were: written agreements for engagement between stakeholders and patients/patient organisations that permit the creation of an equal partnership for all involved; detailed compensation recommendations and templates for ensuring fair and appropriate compensation or reimbursement; detailed policy rules on handling competing interests and conflict of interest statement templates; rules of procedure and tool(s) for identifying and connecting interested parties for PE activities (e.g. “matchmaking”). Matchmaking methods and processes are particularly noted as a gap for HTA bodies.

The interim results here are reflected in outputs elsewhere within the consortium (i.e. survey and focus group work that has been undertaken). At this stage only high level gaps in PE can be identified or implied. The granularity of where those gaps lie, on what level, and to what extent, are beyond the scope of this report. The next steps will be to integrate this new information to further develop a tool with which to better qualify and quantify known and unknown gaps. The inventory that will be eventually created will be able to expand upon the details of some of those known gaps, clarify further some of the gaps that exist that are being addressed in related work in other initiatives and where complementary work could continue, and gaps that are either unknown or poorly recognized. All of this new information can create a focal point for future consortium efforts to address.

2. Introduction and Key Objectives

The overarching mission of the PARADIGM consortium is to provide a framework that allows structured, meaningful, sustainable and ethical patient engagement (PE) throughout three key decision-making points of the development of medicinal products namely: Research priority setting, Design of clinical trials, and Early dialogues with regulators and HTA bodies.

The aim of work package 2 (WP2) is to contribute to this overarching objective through the following:
1. Identify and collate existing practices (that include frameworks, guidance and guidelines) processes (that include protocols, methods, tools or templates) alongside case studies that are relevant to patient engagement initiatives in medicines development (patient driven and non-patient driven);
2. Classify further the PE initiatives through detailed assessment against the criteria developed in work package 1 (i.e. needs and expectations for effective PE);
3. Perform a gap analysis of existing PE initiatives (as defined above) to compile an inventory of quality criteria, which are currently lacking or sub optimally addressed (for example, representativeness and diversity; accommodation for special populations such as young people or people with dementia, etc) during patient engagement

The purpose of this document is to provide an interim report which represents a snapshot of existing PE in medicines development with a representative focus on the 3 decision making points, and the vulnerable populations addressed by the consortium, combined with a high level overview of the analysis to date around existing PE practices and processes. This interim information is not designed to be exhaustive or conclusive as to the status of PE in medicines development. A parallel objective has been the development of a tool which will be used to measure gaps in practice and process – the development of which utilizes the outputs in this report (see appendix for methods). Further detailed interrogation of the initiatives identified here will be undertaken during the next stages of work.

3. Methods

3.1.1 Moments of engagement in medicines development

Here we use the PARADIGM definition of patient engagement as;

"…the effective and active collaboration of patients, patient advocates, patient representatives, and/or carers in the process and decisions within the medicine lifecycle, along with all other stakeholders when appropriate."
We also use the definitions of the three moments of engagement in medicines developed as ;(1)
1) Research and priority setting: providing opinion, providing evidence and/or being part of a group that decides what is important to research
2) Clinical trial design: including, but not limited to, designing protocols, discussing patient burden, discussing patient-related outcomes
3) Early dialogues with regulators and Health Technology Asessment (HTA) bodies: early discussions between industry, HTA agencies and regulators to discuss developmental plans for a medicinal product and to ensure they meet the requirements[1].

[1] * *Early Dialogue is not a decision-making time for any party. In practice it more closely resembles consultation with the chance for feedback and input (two-way communication).*
[2] This represents a joint action with WP4 as part of their scoping and review exercise for which the basic framework(s) for the tools, templates and guidance will be developed and based upon.

3.1.2 Defining 'practices and procees of patient engagement' that will be interogated - Frameworks, practices processes and case studies

Firstly, through consensus building, the working group agreed upon the definitions of the types of PE that cover medicines development which would be interrogated by this working group. Briefly, this formed 3 levels of information in descending order of detail and applicability (Fig.1);

a) Level 1: Frameworks, guidance and guidelines, including those that may also contain additional tools embedded in them
b) Level 2: Processes – tools, SOPs, process, protocols and templates
c) Level 3: Individual case studies that describe in part or wholly the PE activity start to finish

Level 1 has the broadest applicability as the key concepts and principles of PE are described. Level 2 has some increased specificity as it describes in more detail the practical application of Level 1 concepts as key steps or methods. Level 3 describes in part an individual PE activity or experience, thus has the least generalisability to it. These examples can however provide key insight into emerging or successful practices or processes, especially in specific diseases, vulnerable populations (i.e young people and, people with dementia and their carers), and decision making points, that can be used to better assess currently what actually happens today, set against what is expected or needed to happen (according to the reported preferences, needs and expectations – see D1.1 report).

As a second stage these definitions were used as part of the inclusion/exclusion criteria in section 3.3.

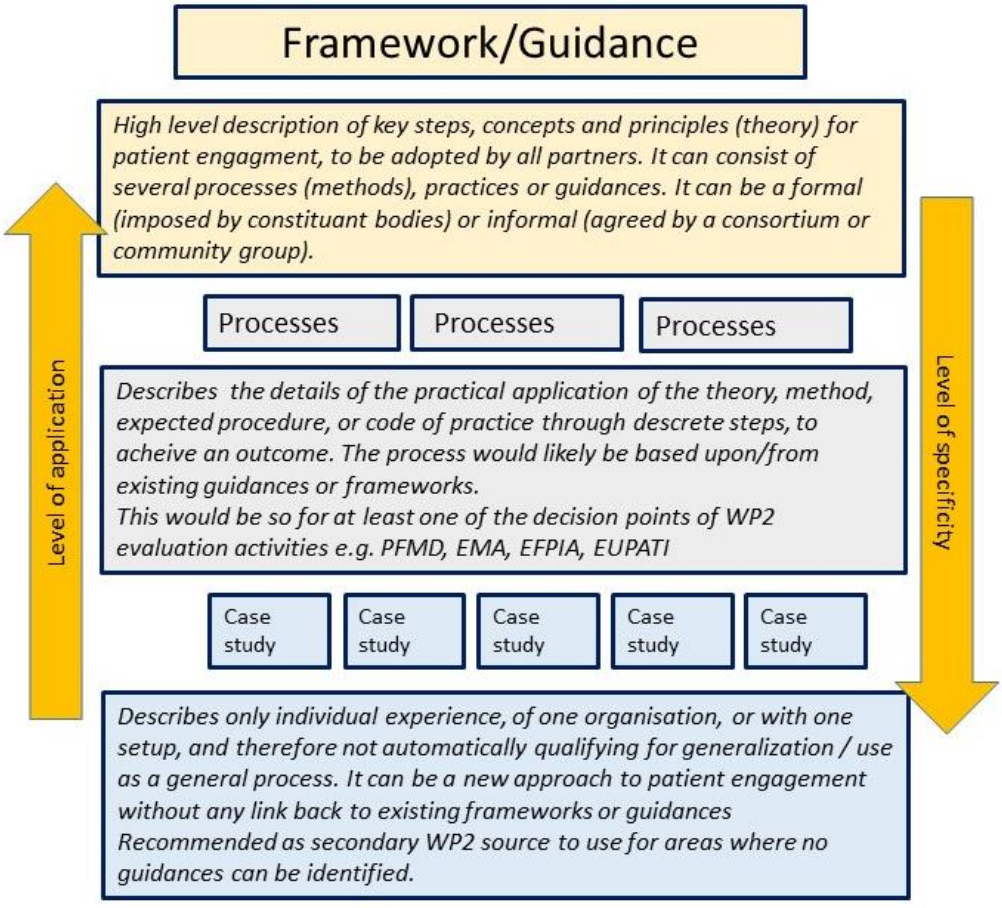


Figure 1: Schematic of definition of i) framework, guidance and guideline, ii) processes and iii) case studies for WP2 data gathering and interrogation

3.2 Data gathering of examples of practices and processes

A two-step selection approach was followed. Firstly, high level summary information (English only) relating to each PE initiative of interest was exported from two existing consortium PE platforms - Patient Focused Medicines Development (PFMD) (2), and the European Patients Academy (EUPATI) (3). Initial criteria were that each initiative must be related to PE in medicines development (rather than for example health service delivery) with additional inclusion/exclusion criteria subsequently applied (see below). As a second phase, additional initiatives were identified and gathered from recent European Federation of Pharmaceutical Industries and Associations (EFPIA) sources such as the 2016 and 2017 Health Collaboration Guides (4, 5). Through snowball methods of data gathering with other consortium members and through discussions with various relevant Paradigm International Liaison Group (PILG) members, further initiatives of potential interest were identified and shared by the respective partners: Clinical Trials Transformative Initiative (CTTI), TransCelerate, and Patient-Centered Outcomes Research Institute (PCORI) (6-8). Examples from CTTI and TransCelerate were included. As PCORI projects largely focus on comparative effectiveness research (CER) and patient reported outcomes (PROs) in healthcare delivery settings, no case examples were included. The PCORI rubric (9) and other general learnings were, however, shared and included within the analysis. A number of further case studies were identified and included here from outside of those sources mentioned above. These were identified through some individual organisations (that include industry and HTA), and some country specific examples (mainly Dutch). These case examples will be assessed further together during the future gap analysis.

3.3 Decision tree inclusion/exclusion criteria

The initial high-level identification of PE initiatives in medicines development resulted in >300 of potential interest. In the second step of the selection process in order to both increase the relevance of the identified initiatives to PARADIGM and to arrive at a more manageable number to perform a detailed analysis on, the working group agreed on additional selection criteria that were applied to the initial list. Based upon a high level review of publically available information each of these 3 criteria must have been met in order to continue to consider a particular PE initiative for further interrogation (see Fig 2). These were:

1) Were patient(s) or patient groups directly engaged?
2) Is the PE activity part of a i) framework, guidance or guideline, ii) process, or iii) case study?
3) Does the framework/process/practice or case study cover 1 or more of the 3 decision-making points?

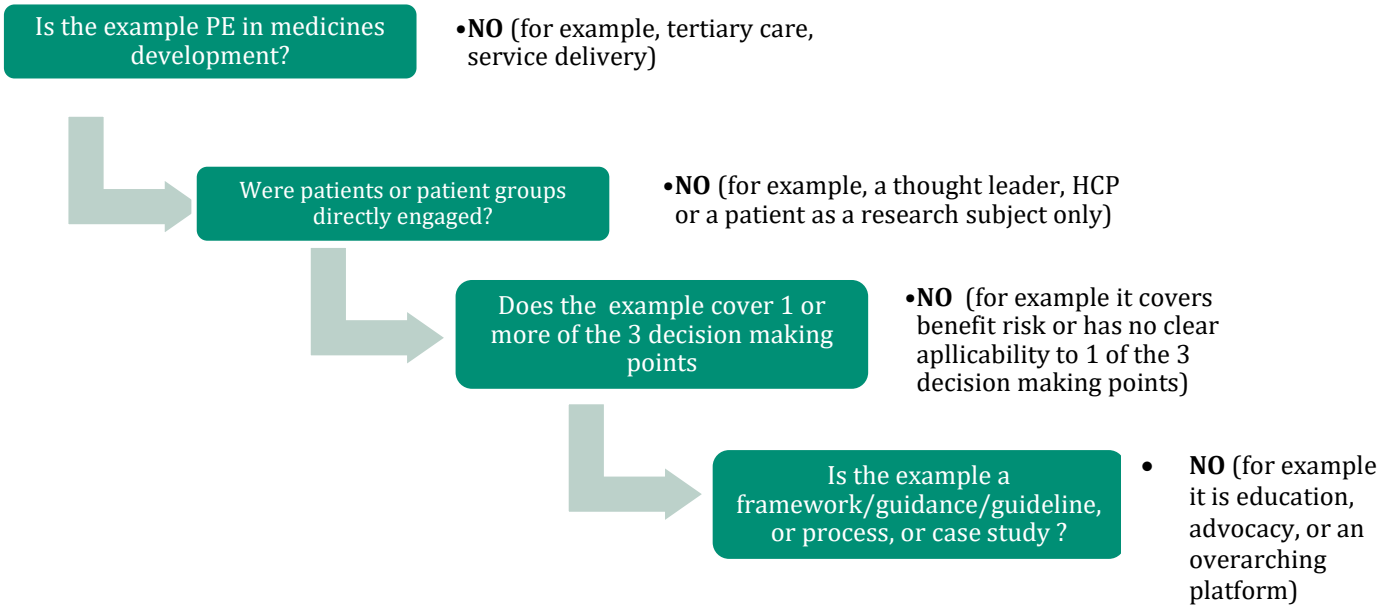


Figure 2. Schematic of decision tree of inclusion/exclusion criteria for selecting PE initiatives of interest forward for further detailed analysis

Several reviewers cross-checked the application of the above criteria to the list of initiatives. Any conflicts were resolved by consensus. Some examples of where exclusion of an initiative occurred were as follows; the initiate only covered a down-stream decision making point (i.e. post market access or benefit-risk) with no clear application to at least one of the three decision making points of PARADIGM, the initiative was clearly general education or advocacy, or patient or patients groups were not clearly engaged in the process or initiative – rather it was, a thought leader, healthcare professional, or solely being a subject of research.

3.4 Descriptive analysis

Descriptive data were gathered based on a high level review of publicly available information on each initiative, found on initiative websites and PFMD, EUPATI and PILG platforms. Where the information was reported as such on the website or platform, or was readily identifiable, each initiative was characterized by several themes:

a) Type of PE activity: i) Framework, guidance or guideline ii) Processes (SOPs, protocols, tools, metrics or methods to measure outcomes), iii) Case studies (projects, programs, initiatives of individual examples of PE activity), b) Decision making point (s) covered or clearly applicable to, c) Disease or therapy area (s) covered, d) Geographical coverage (self-reported or the majority nationality of patients involved, e) Specific inclusion of vulnerable populations (for example young people, people with dementia and their carers, rare diseases, etc).

To complement the descriptive analysis, a targeted sampling approach was conducted to identify some of the key frameworks and guidance that originate from different stakeholder groups - specifically: patient groups (AE, INVOLVE)(10, 11), PFMD's PE Quality Guidance and tools (12), EUPATI's 4 guidance documents (13), the pharmaceutical industry (EFPIA guidance and codes of conduct) (14), regulators (EMA, FDA)(15, 16), reimbursement agencies (HTAi and NICE, UK) (17, 18), and HCPs (WHO) (19). A review was conducted in order to:

1) Identify if different stakeholder groups have different priorities in their defined practices and processes
2) Identify common practices and process against which gaps in practices can be measured during a future gap analysis (i.e. the comparison of actual performance with potential or desired performance).

And lastly through a joint action with other consortium members, a list of some additional 'known' deficiencies or gaps in PE practices were identified taking into account the methods and stakeholders involved in creating these documents (i.e. from the described methods and anecdotal knowledge of consortium members) and a brief review of the literature of existing tools and templates[2]. The summary results are included here also to complement the descriptive analysis.

4 Descriptive Results

Initially >300 initiatives were identified from the existing platforms and additional scoping exercises with PILG members and other sources. After applying the aforementioned inclusion/exclusion criteria, 165 examples were considered suitable for further interrogation and gap analysis.

4.1 Common descriptors of frameworks, processes and practices/case studies

In the selected sample nearly two thirds of initiatives focus on PE in the design of clinical trials (59%). Approximately one fifth cover each of research priority setting (16%) and early dialogues with regulators and HTA (12%) – only 5% appear to cover the entire medicines development continuum (Figure 3A). Equal numbers of initiatives were categorized as either high-level framework, guidance or guideline for PE or as specific processes to enable PE (each 12%). The remaining three quarters (76%) were categorized as individual case studies (Figure 3B) that contain varying degrees, of information on the processes and outcomes of the PE activity.

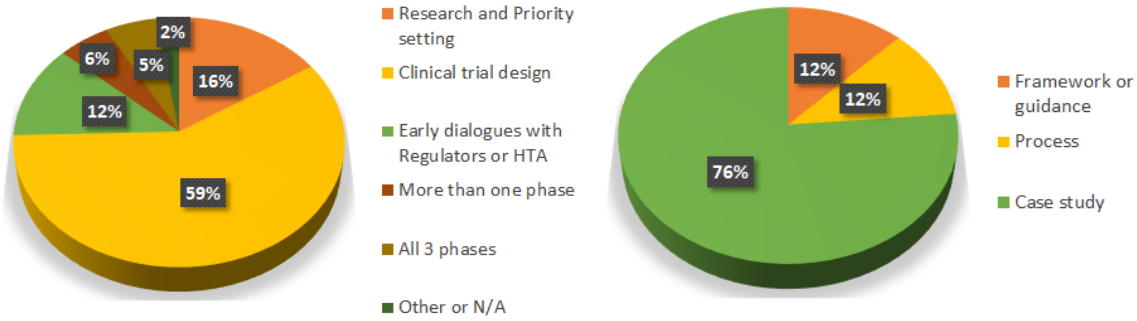
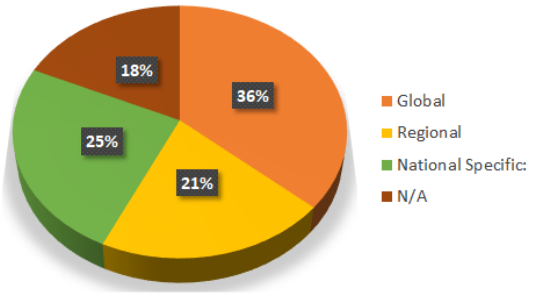


Figure 3A and 3B – Categorization of 165 selected PE initiatives for phase in medicine development (A) and by the format of outputs.

[2] This represents a joint action with WP4 as part of their scoping and review exercise for which the basic framework(s) for the tools, templates and guidance will be developed and based upon.



Most initiatives appeared to have a global coverage or application (36%). Of the regional specific initiatives nearly all were European. Of the initiatives with national coverage ~25% come from the UK and USA each – others from France, Spain, Switzerland, and Australia (Figure 4).

Figure 4– Categorization of selected PE initiatives by geographical coverage or application

A majority of initiatives are disease area specific (44%) (Fig 5A), of which nine initiatives covered Parkinson's or Alzheimer's conditions, six cover specific cancers (i.e. breast cancer), with others covering additional chronic illness (e.g. lupus and psoriasis). Less than 10% covered broader therapeutic areas (e.g. rare diseases). Over one third (39%) of initiatives appeared to be non-disease specific; applicable across all conditions (Fig. 5B). Nearly three quarters (73%) appeared to include or be applicable to the general adult population. There were very few examples (<10%) that specifically included young people, elderly populations, or parents and carers into the PE initiative (Fig 5B).

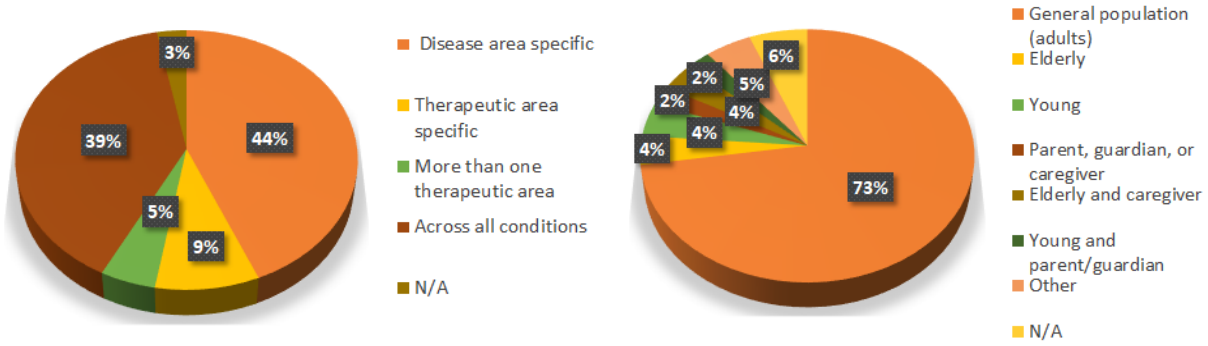


Figure 5 A and B Categorisation of selected PE initiatives by disease or therapy area (A) and the population (s) of coverage (B)

4.2 Framework, Guidance and Guidelines

4.2.1Common elements across frameworks and stakeholders and time points

Most practices define *what to do* - concepts, general guidance (current, or desired) as *'rules of engagement' or 'best practices'* - but not *how to do it*. These practices range from potentially being applicable (in part or whole) across the entire value chain from R&D to post approval (for example, PFMD's Quality criteria), with just a few that are applicable to specific decision-making points or specific stakeholder groups in the value chain (for example, EUPATI's 4 guidance documents for industry, regulators, ethics committees and HTA bodies). Notably the EMA's framework "Revised framework for interaction between the European Medicines Agency and patients and consumers and their organisations" (15) is aimed, as the title indicates, specifically at patients, consumers and their

organisations and covers a specific decision point which is the regulatory activities of the EMA where patients/patient organisations might be involved.

Common themes identified within frameworks and guidance/guidelines were:

1) Defining the objective of the planned interaction and/or areas of common interest ("shared purpose")
2) Establishing/defining roles and responsibilities
3) Ensuring transparency in all processes (publicly availability of who, what, when and finances)
4) Providing compensation for time/costs and help with logistical planning
5) Building capacity and capability (for patient's to be effective contributors and for stakeholders to engage effectively with patients)
6) Optimising insight generation from patient experiences and knowledge of living with the disease

A few examples of guidance standout among the others so far - those being from PFMD, EUPATI, and EMA. The PFMD and EUPATI examples both cover the whole R&D process and therefore address all three decision-making points, which PARADIGM has prioritized. Both have been jointly created with patients, included large numbers and breadth of experts, utilised repeated cycles of validation with some other stakeholder groups, and were appropriately validated through public consultation. These examples show no obvious gaps across the medicines lifecycle continuum. PFMD Quality Guidance also provides a step-by-step approach to PE and is supported by additional templates to assist with 1) planning PE activities, 2) quality and impact assessment, and 3) gap analysis (12). In comparison, another well designed guidance, the EMA "Revised framework for interaction between the European Medicines Agency and patients and consumers and their organisations" is well structured for a specific stakeholder organisation, the agency (not addressing National Competent Authorities), and focuses specifically on regulatory deliberations. The practices published by EUPATI are also prime examples of co-creation together with the respective stakeholders like regulators (e.g. EMA) and HTA (e.g. NICE); a factor which is expected to have positive impact on the acceptance and implementation of the practices. Furthermore, all these frameworks and guidance are available on public platforms or published in peer-reviewed journals (e.g. EUPATI guidance is in Frontiers (20)) and are updated periodically to reflect the changing landscape.

The following sections summarise some general and specific themes that emerged from the data as to current deficiencies or gaps in PE across the landscape, at the 3 levels described earlier.

4.2.2 High level deficiencies identified in frameworks, guidance and guidelines

Most frameworks and guidance's do not provide the link between a high-level of *what to do* with a step-by-step *how to do it* for a PE activity from start to finish (e.g. methods needed or when to use them). There were a few examples that were accompanied by supporting tools and templates covering some elements within the guidance (for example how to plan a PE activity or record it included in PFMD's Quality Guidance), but most lack this detail. This means that the application and implementation of the guiding principles are vague and ill-defined. In comparison to the frameworks that spanned the full medicine development continuum, there were few that covered specific decision-making points (e.g. research priority setting) that could account for the different input required from patients, the basic knowledge required to impart effective input, and the format of those interactions at that specific point (EUPATI's 4 guidance documents being an exception). Where they exist, they were predominately covering the clinical trial design phase. Similarly, with a few exceptions (for example, INVOLVE, and EMA's involvement of young patients/consumers (21)), frameworks appear to be applicable across all conditions and populations (mainly adult). Those applicable to vulnerable populations, though, are largely lacking by comparison.

For example, overall guidance for involving people with dementia in PE appears to be lacking entirely at this time (see the position article for details(10)). Furthermore, with the exception of a few good examples there is minimal guidance for patient support to better understand HTA and regulatory mandates, processes and decision making (see examples from EMA (22, 23) and HTA; HTAi and NICE). What does exist often lacks sufficient detail to fully address; legal requirements such as consents, child protection, incorporation of parent and carer considerations and input, and confidentiality, which can specifically account for vulnerable populations of focus here (e.g. young people and people with dementia).

Most frameworks suggest a pragmatic approach by working groups - typically involving lay people, researchers and/or research funders - over an undefined period, with undefined or loosely defined methods (e.g. feedback, surveys, and consultation). Many of the frameworks lack documented recourse to the academic literature on lay involvement (i.e. frameworks and methods for effective PE or Patient and public involvement (PPI). Most approaches also appear to be experiential or based at least partially on other stakeholders' previous experiences or frameworks (e.g. EMA). Furthermore, there are very few examples that support how to measure PE and its outputs/outcomes. Only documents from regulators (EMA) and HTA (HTAi) give some guidance that measuring the implementation of the PE activity is a necessity and, in the case of EMA, how to report on the impact of PE on their activities (see WP3 publication T3.1).

Considering a reported high number of guidance documents developed, and a clear reported need for them, there is also a surprising lack of published or publicly available guidance across the board. The recent peer reviewed publication of the EUPATI (20) and FDA's Patient Focused Drug Development (PFDD) guidance documents (16) could be seen as a signal for a change to more transparency.

4.3 Process and case studies

4.3.1Common elements across processes, case studies, and stakeholders and time points

In comparison to guidance on *what to do* there is a relative paucity of exemplars of *how to do it,* especially to effectively plan, implement and support a given PE activity from start to finish with contextual and temporal application. This could partly be explained by the fact that we only searched for available English written documents - we are unaware of available *how to do it* guidance's in native languages.
Some good examples exist of more detailed step-by-step guidance and templates that can help facilitate and manage certain aspects of a PE activity. One example is the involvement of patients in the design and implementation of cancer clinical trials - SWOG Patient Advocate Guide(24). It provides good step-by-step information to patient advocates on how they can get involved, timelines, training and even tips on the types of questions they can expect. When it comes to individual case studies, we observe an increase in the types of patient engagement activities across the value chain and across diverse stakeholders. One worthy example in the rare disease space is the public-private partnership, DevelopAKUre for alkaptonuria. DevelopAKUre is patient-led, with the AKU (Alkaptonuria) Society as a lead partner, ensuring patient views were considered at planning stages, and throughout the ongoing studies. The AKU Society now leads on patient recruitment and support, developing patient information documents and promoting patient retention (25).

4.3.2 High level deficiencies identified in processes and case studies

Some of the known deficiencies in processes identified are that they appear to have limited application outside of a given stakeholder group, decision making point or therapy area (either explicit or implicit in the content or how it was developed and validated). In the instance of case examples, generally they are often missing details of the start-to-finish process or methods (what was done, how, and when, and including pre and post engagement phases), or are not publicly available for all to leverage. There are some processes that are quite high-level and are missing supporting tools and templates that empower parties to take action; for example, how to find patient partners for engagement. Moreover, most processes do not specifically focus on or give additional steer on the specifics of the involvement of vulnerable populations -for example, specifics of the condition, specific methodological considerations during the planning and implementation phases, appropriate methods of communication and feedback, etc.

There are some more general deficiencies in the rules of procedure and tool(s) for identifying and connecting interested parties for PE activities ("matchmaking"); for example, an accessible database, covering various stages of R&D and disease level expertise. This is particularly noted as a gap for HTA bodies. There are gaps in templates for written agreements for engagement between stakeholders and patients/patient organisations that permits the creation of an equal partnership for all involved; for example, defining a description of the activity and its objectives, the nature of the interaction during the activity, consent (if relevant), release, confidentiality, compensation, data privacy, compliance, declaration of conflict of interest, and timelines.

Detailed compensation recommendations and templates are lacking for ensuring fair and appropriate compensation / reimbursement for the type of engagement, such as: direct payment for travel, total time invested plus expenses, costs incurred by patient organisations when identifying or supporting patients for engagement in activities (e.g. peer support groups, training and preparation), indirect benefits in kind (e.g. the patient organisation providing services free of charge), or any other non-financial benefits in kind provided to the patient/patient organization (e.g. training sessions, agency services, the setting up of websites). Some existing resources and ongoing initiatives to better support compensation do exist. Noteworthy examples are, the PCORI Financial Compensation framework(26) which is applicable to the North American region. The EMA and INVOLVE cost calculator(27) are applicable to EU region and WECAN (28) are starting to develop new guidance for fair market value based on a recent EU survey. However, there appears to be additional needs to consider, and methods to support "fair" amounts of compensation, legal boundaries, taxes, etc. that are applicable to, or can be adapted for national level considerations and laws across EU member states that could be different from the above. Further work within the consortium will take into account the emerging work from some of these above initiatives.

Detailed policy rules on handling competing interests and conflict of interest statement templates are also largely lacking at the EU level. For example, consideration in the differences in definition of direct vs. indirect interest, categories of interests, process rules of handling declarations, and control. A good existing example to learn from is the EMA's policy on the handling of competing interests of scientific committees' members and experts (23). How this and similar examples could be built upon to better account for competing interests at the 3 different decision making points and/or vulnerable populations would be of value to address later in the project.

When it comes to case studies, generally there is information lacking particularly on the depth of patient engagement during the PE activity (e.g. were patients informed, consulted or fully involved in co-creating the project and its outcomes?), and often platforms that orchestrate dialogue between various stakeholders and registries that capture patient data are inappropriately coined as 'patient engagement', compared to how PE has been defined within PARADIGM (see definitions). This could be partially due to a lack of a common understanding of the definition of PE. Additionally, there are few case studies that are focused on involving carers and vulnerable populations like people with

dementia and young people, or that involve early dialogues with regulators and HTA. An explanation for the lack of detail could be that, case examples are part of an evolving or ongoing experience, often in a single population, hence full details may not yet be available. This makes translating the learnings into a broader context much more difficult.

5. Discussion

Gaps in *what to do* and *how to do it*

Simply put, this interim analysis can broadly be split into the, what *to do* and, *how to do it.*
With few exceptions there appears to be a disconnect between guiding principles, and the details of how to undertake PE start to finish coupled with the supporting tools and forms to specifically manage elements of a PE activity (i.e the three levels of application - framework, methodology and forms). The applicability of a guidance that covers the entire medicines R&D chain and applies to all stakeholders' versus one that covers a specific decision-making point and/or stakeholder group is a double-edged sword. The former can lack the specificity and applicability to a specific decision-making point or stakeholder group where for example, patient input and knowledge will be different (e.g. young people and people with dementia), and the later relies too much on the phrase, "adapt X to your needs". This later point can be particularly unhelpful, as it can lead to ambiguity in interpretation, divergence from and poor adherence to, the underlying guiding principles. What is largely missing in guidance and tools that are applicable more broadly is the additional information and methods directing the user as to what elements of the guiding principles could be adapted and how they can be adapted to suit the situation or stakeholder at hand.

As it stands currently there appears to be even more gaps in readily available detailed process, tools and templates to support PE from start to finish. While it is acknowledged that where information is not readily available does not categorically constitute a gap in PE, if any element of the PE process that was undertaken is not documented, it does. For example, if roles and responsibilities of all parties undertaking PE activity were not documented as planned, implemented and acted upon, that constitutes a gap in reporting processes, which could be rectified with better tools, templates and guidance's of what to do, how to do it, with who, and when. Case examples hint at some good exemplars with which to build upon. However, acknowledging that they are by definition, individual experiences, case examples often lack a clear link back to any available or recognisable guiding principles, methods or literature. Templates covering contracts for fair compensation, templates for how to address potential conflict of interest issues, and detailed methods for measurement of return on engagement are often limited in their application or missing entirely (as also shown in the review of WP3 T3.1).

It can be hypothesised that the reasons for so many gaps are multifaceted. Overarching frameworks and guidance are developed to fit a need. If the need is not perceived, regardless of whether robust internal SOPs or processes exist, current practices prevail. The number of examples excluded here even in our targeted search that did not cover medicines development but broader social sciences and advocacy was three times as many compared to those that did. Patient engagement has many contextual applications with relatively few covering medicines development and even fewer directed at two of the three decision-making points (research priority setting and early dialogues) or vulnerable populations we are considering here. Moreover, by making frameworks more overarching, much of the contextual information - which is particularly desirable - will be lost (for instance, how to meaningfully engage a specific vulnerable, and hard-to-reach patient groups).

At this stage of our review, while guidance's are generally publicly available as are some tools, by comparison, protocols, processes and templates used by the various stakeholders to implement and manage a PE activity are lacking, and those that are publicly available for others to leverage, even

more so. This suggests that existing processes, protocols and tools are either informal in nature, poorly adhered to, that stakeholders are not able or willing to share their learnings outside of their organisation, or that no documented internal protocols or templates exist (With the exception of some regulatory agencies (EMA, FDA) and some HTA bodies (e.g. NICE). Any of these hypotheses present clear gaps that can and should be extrapolated further, in order to fulfil the needs and preferences for more effective PE that will have been identified by the consortium.

These interim findings here are reflected in the results of the consortium survey. The most commonly reported wish or request in order to improve PE was i) for metrics to demonstrate value (covered by WP3) and ii) new methods (tools, templates) to better support almost every aspect of PE activity – as reported here, concrete examples of these are relatively few, not recorded, or are unavailable to the wider community. Additionally, the survey reported that while some stakeholder groups have internal SOPs for PE (e.g. industry and HCP) they were not always used. Other stakeholders reported a general lack of standard or useable SOPs specific to their stakeholder group or the decision-making point(s) for which PE regularly occur (e.g. regulators and HTA).

Next steps

This interim report is neither intended to be exhaustive or complete as yet, but provide an initial consolidation and preliminary assessment of existing practices and process for PE in medicines development. It permits a high-level snapshot of the current PE landscape and where some of the known gaps or deficiencies exist in *what to do* and *how to do it*. At this stage this confirms anecdotal evidence of some of those known gaps and gives more credence to others which have been long thought of but not collectively articulated. The next steps here will be several fold: i) to provide interim analysis to inform the development of other consortium partners' deliverables, ii) incorporate additional consortium learning that will inform our future analysis, and iii) in parallel provide input into the testing and validating the a tool that is able to generate more detailed information of the gaps in PE (see Appendix for brief methods for the exploration of first gaps is described). It is intended that the final output of this work package will inform what the major gaps are (known and unknown), where and why they exist, and create a focal point for future efforts to address.

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Appendix

Below is a brief methodology for utilizing the D2.1 short report, known gaps and common elements from existing practices and process in order to help develop the tool to be used for gap analysis (i.e. the comparison of actual performance with potential or desired performance). The development of this tool is ongoing and in parallel to the work described in this report.

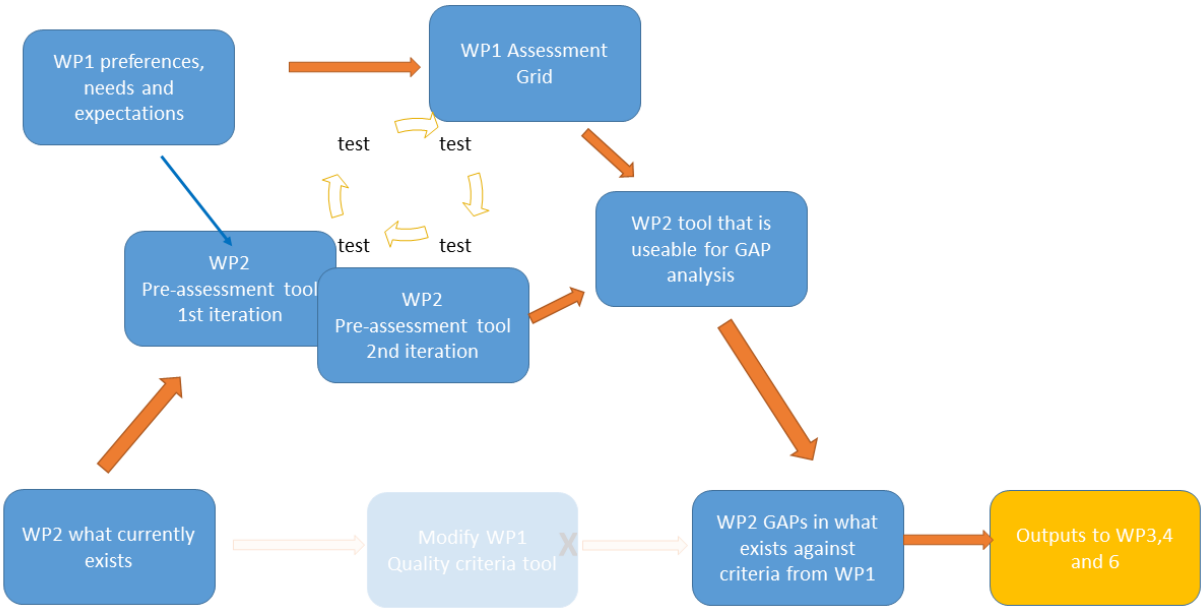

Fig 6 Schematic of the cycles of iterative design, testing and validation of the tool to be used for GAP analysis based on integrating outputs from consortium partners

In order to start planning for the comprehensive gap evaluation of identified PE initiatives a first tool iteration (Fig 6) has been developed to start considering how gaps can be comprehensively evaluated and summarised moving forward.

The initial (pre-assessment) tool consisted of eight questions based on the six common themes reported in Section 4.2.1. Apart from overall detail about the initiatives (and classification into the decision-making point it covered), the questions tried to evaluate roles and responsibilities, transparency, compensation, capabilities, and implementing outcome. The questions also requested suggestions of new gaps not currently being measured for ("*unknown gaps")* and new ways of measuring gaps.

The first iteration of the tool, containing eight questions, was then tested by six separate volunteers from WP2, who used the tool to assess six different initiatives - PFMD Quality Guidance, EUPATI Guidance for stakeholders, iCAN, and examples from industry partners GSK, Amgen, and UCB example. In parallel, a workshop of independent experts was held in Brussels (Oct 2018) and the participants were asked to describe gaps as they see them and to propose how to measure / evaluate those gaps.

From the initial testing of the tool and the workshop 30 themes have emerged via qualitative review. These themes are currently under evaluation alongside the quality criteria generated from the Delphi process, with the emphasis on how to redact them, and how to ensure that the important ones will be

incorporated into the next iteration of the tool in a way that keeps the tool simple to use but also ensures the generation of valuable data / insight when conducting the planned evaluation of the PE initiatives. To make it sure the tool remains feasible and structured but also 'valid', the tool will be embedded with an available and validated framework on process criteria (Athena Institute).

It is planned to identify an electronic solution suitable for deploying the tool to most efficiently capture the gaps during the evaluation process. Exploring options for this is underway and will be finalised for the next iteration of the tool.

Lead contributors to Deliverable 2.1

UOXF-CASMI	AE	Amgen	Servier
Bayer	FSJD	Synergist	Lundbeck
EATG	Novartis	SARD	Pfizer
VU-Athena	IACS	Roche	EURORDIS
UCB			