Patient and Public Involvement Toolkit

Antimicrobial Medicines Development Research

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Contents

1 Introduction

Members of the public possess invaluable first-hand subjective knowledge of the severity of disease, symptoms, and how these impact their quality of life. Patient and public involvement (PPI) in medicines development is increasingly being recognised as not only good to have, but should be the foundation on which research, regulatory reviews, and decisions rest (Borup *et al.*, 2016). The use of the public's knowledge and 'lived experience' ensures more focused, relevant and meaningful medicines development by the pharmaceutical industry, and provides new insights to aid the decision-making process by regulatory authorities (ibid). Over time, the pharmaceutical industry has realised the potential benefit of PPI in securing the sustainability and profitability of medicines development research (Parsons *et al.*, 2015).

Besides, involving the public in any decision that affects their health is ethical, and helps create a culture of openness, transparency, inclusiveness, and credibility. Those who are involved as public contributors themselves report an increased sense of wellbeing through being able to contribute to the greater good of society (WEAHSN, 2016). Other potential benefits of PPI in medicines development research are summarised in Table 1a.

Table 1a: Potential benefits of PPI in medicines development research (Geissler *et al.*, 2017)

Benefits to the public	Benefits to the research
Ensures research and its outcomes address patients' genuine unmet needs	Ensures research and its outcomes address patients' real unmet needs, and not professionals' perception of patients' needs
Increases/strengthens knowledge and research skills	Improves patient-related material, e.g. information sheet
Greater empowerment and confidence to actively contribute to the research process	Potential to improve response rates and recruitment
Opportunity to utilise patient experience and knowledge on their condition	Improves trial design or elements, e.g. priorities, research questions, data collection methods, etc.
Acceptance of the public as equal partners in the research process and increases sense of ownership of the research	More patient-relevant research methods and findings
Improves access to funding to put topics on the research agenda that may not have otherwise be taken into consideration	Challenges the assumptions made by researchers
Increases understanding of the nature and purpose of clinical trials	Wider dissemination of findings
Improves understanding between the public and researchers	
Promotes development of medicines that are more representative of patients' needs	
Enables data and information exchange between patients and industry on the realities of medicine use and management	

1.1 Toolkit overview

PPI is a rapidly growing and important global movement. A non-exhaustive list of organisations from across the world that are advancing PPI in medicines development research is available in Appendix 1.

PPI specifically in antimicrobial medicines development research, however, is new and unfamiliar. There is currently a lack of literature and clear practical guidance focusing on PPI in this area (Evans *et al.*, 2017). Given the short-term nature of many microbial infections, there are few established patient support groups or voluntary organisations in the field of infection sciences. In view of the increasing costs of medicines development and the financial consequences of market failure, early incorporation of PPI in research may reduce waste of resources (Geissler *et al.*, 2017).

COMBACTE-MAGNET is a consortium funded by the Innovative Medicines Initiative (www.imi.europa.eu) Joint Undertaking and EFPIA (European Federation of Pharmaceutical Industries and Association) companies seeking new ways of treating multi-resistant bacterial infections. As part of its clinical coordinating work package, **WP6i**, we have developed this toolkit to provide systematic and evidence-based guidance on how and when to involve the public in medicines development research, in particular antimicrobials.

Toolkit content is presented as individual chapters, allowing you to select and read topics that are relevant to you. Individual chapters may be read online or downloaded from the **Library** section of the COMBACTE website www.combacte.com. This toolkit may be updated from time to time, and further information or examples added. Training workshops to support the use of this toolkit may be available.

Please contact Andy Gibson at andy.gibson@uwe.ac.uk for more information about this toolkit or to arrange for a toolkit training workshop.

1.1.1   What is PPI in research?

For the purposes of this toolkit, PPI in research refers to research that is carried out **'with'** the public rather than **'to'**, **'about'** or **'for'** them (INVOLVE, 2012). PPI is different from:

- public *participation* in a research study or clinical trial; or
- public *engagement* through provision and dissemination of information about research

PPI is an **active** involvement of the public in the research process, for example:

- as members of a patient panel, patient advisory group or steering group
- as individual research partners or co-researchers
- identifying research priorities
- advising on the patient recruitment strategy
- designing and reviewing patient-related material , e.g. informed consent form

The term **'public'** used in this toolkit includes patients (past, current, and potential patients), carers, parents/guardians, and people who use health and social care services (or the organisations that represent them). Where it specifically relates to users of medicines, e.g. antimicrobials, the term **'patients'** may be used instead.

1.1.2 Who is the toolkit for?

This toolkit is primarily for principal investigators, research teams, and pharmaceutical companies. It is also potentially useful to other academics and public contributors.

Due to the lack of literature on PPI in antimicrobial medicines development research, most of the case examples included are from various other fields, such as rheumatology and mental health. Therefore, this toolkit is not only for those involved in the research and development of antimicrobials, but can be applied to medicines development in general, and potentially to other areas of acute clinical research.

1.1.3 What is in the toolkit?

The topics covered in this toolkit are:

- **The basics of PPI**: How is PPI conceptualised. Who and when to involve people in the medicines development lifecycle.
- **Creating links with patients and the public**: How to find the appropriate people for PPI. What the ethics and consent processes around PPI are.
- **Planning and preparing for PPI**: What strategic planning is involved, i.e. what the organisational responsibilities are. How to plan and prepare for PPI (i) costs and payments, (ii) training and support, and (iii) meetings.
- **PPI in the medicines development lifecycle**: What the role of PPI at different stages of the lifecycle is, i.e. setting the research agenda, drug discovery and preclinical development, clinical trials, regulatory review and approval, and antimicrobial stewardship.
- **Approaches to PPI**: How to carry out PPI through consultation and collaboration.
- **Evaluating PPI**: How to evaluate the process and impact of PPI.

This toolkit also includes:

An abstract at the start of each chapter, describing its content.

Tip boxes on how to, e.g. find public contributors for research?

Case examples on, e.g. PPI in identifying outcomes that are meaningful and relevant to patients.

Key points to summarise the content of each chapter.

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1.3 Acknowledgements

Please cite this work as:

Kok M, Gibson A, Evans D, Grier S, MacGowan A, and members of the Patient and Public Involvement Panel for Antimicrobial Drugs (2018). *Patient and public involvement toolkit for antimicrobial medicines development research.* University of the West of England.

ISBN 9781860435461

2   The basics of PPI

ABSTRACT

Because people may have such different understandings of PPI, it is useful to think about how it can best be conceptualised before engaging in it. We find the most helpful way to think of PPI is as a conversation or knowledge space, where researchers and the public exchange ideas, values, assumptions and experiences. Gibson *et al.* (2017) depicts this knowledge space as a four-dimensional 'cube', which forms a framework useful both for planning and evaluating PPI.

This chapter describes how the *'cube' framework* can be used as a planning tool for PPI in research. We discuss the question of who to involve, addressing the common issue of *'representativeness'* in PPI and considering the role of *'lived experience'*. We also consider how to involve people at every stage of the antimicrobial medicines development lifecycle to maximise the impact of PPI. Finally, we present the first of our Tip Boxes, starting with tips on "How to have effective PPI."

2.1   Conceptualising PPI

Because people may have such different understandings of PPI, it is useful to think about how it can best be conceptualised before engaging in it. PPI has commonly been conceptualised as a hierarchy or a continuum (Brett *et al.*, 2010). Arnstein's (1969) paper on the *ladder of participation* is considered to be the first to conceptualise involvement as a series of hierarchical levels. It describes eight levels of involvement, differentiated by the degree to which the public is empowered to participate in decision-making processes, from manipulation at the bottom to citizen control at the top (Brett *et al.*, 2010).

More recent descriptions of the levels of PPI have condensed Arnstein's ladder of participation into three steps:

- *Consultation* – low level involvement, where researchers ask the public for their views to inform decision-making

- *Collaboration* – a more equal, active and ongoing partnership between researchers and the public

- *User-led* – research is controlled and led by the public (INVOLVE, 2012; Boote *et al.*, 2002)

Rather than thinking of the different levels of involvement as a hierarchy, it may be more appropriate to consider them as being more or less suited to different circumstances. For example, consultation and collaboration are more relevant to antimicrobial medicines development research, and are described in detail in Chapter 9. This chapter will focus on reporting the evidence around the conceptualisation of PPI and offer practical guidance on how to have effective PPI, who to involve, and when to involve them. More recent thinking has been critical of seeing PPI as having just one linear dimension, and various multi-dimensional conceptual frameworks or models have been developed. We present one model below which can be used both for planning and evaluating PPI.

2.2 PPI as a conversation or knowledge space

Brett *et al.* (2014) suggested that PPI needs to be considered as a complex *intervention* that requires appropriate evaluation. While acknowledging that PPI is complex and that it is important to evaluate PPI in research and seek evidence of its impact, Staley (2015) argues that it is more helpful to think of PPI as a *conversation* between researchers and the public i.e. an interaction where an exchange of knowledge and mutual learning occurs. When we think of PPI in this way it becomes clear that, unlike an intervention that can be precisely defined and standardised, PPI is variable and highly dependent on context i.e. the environment in which PPI is undertaken, that may include funding, policy, physical environment and the attitude of those involved (Staley, 2015; Brett *et al.*, 2014). Therefore, the outcome of PPI, just like any conversation, cannot be easily defined in advance.

Conceptualising PPI as a conversation emphasises the exchange of ideas, values, assumptions and experiences that takes place between researchers and the public (Staley, 2017). This exchange or interaction of different forms of knowledge (public, professional or scientific) has also been termed a *knowledge space* (Elliott and Williams, 2008). Gibson *et al.* (2017) developed a theoretical model to describe the four fundamental elements for successful knowledge exchange, taking into account the dynamic and fluid nature of interactions within knowledge spaces. The four dimensions of the framework are described in Table 2a and illustrated in Figure 2a.

Table 2a: Description of the four key dimensions of a knowledge space (Gibson *et al.*, 2017)

i.	Weak voice or strong voice	Strong voices discuss issues and influence decision-making. Weak voices may discuss issues, but have little influence on decision-making.
ii.	One way to be involved or many ways to be involved	Knowledge can take on different forms, which may not be equally valued. A single involvement approach is likely to privilege one social/cultural group over another, thus perpetuating inequality.
iii.	Organisation's concerns or public concerns	Public concerns are in the context of social action, e.g. public opinion, norms and values, as well as individual experiences and behaviours. Organisation's concerns are, e.g. bureaucracies and markets.
iv.	Organisation changes or organisation resists change	Decision-makers' willingness and ability to respond to issues raised by participants in knowledge spaces depend on contextual factors, e.g. economic resources and national policies.

It is through these conversations or knowledge spaces that researchers encounter unexpected learning or 'lightbulb' moments that contribute to a more holistic understanding of a complex problem. Therefore, it is important to create conditions that would facilitate good quality conversations i.e. PPI, where meaningful exchange that supports genuine learning can occur, for example by:

- having PPI meetings in a more relaxed environment, such as a community centre instead of a hospital meeting room
- preparing researchers to be ready to listen, learn from, and respond to public contributors
- encouraging public contributors to become confident in "challenging assumptions, and sharing the most relevant aspects of their experiential knowledge" (Staley, 2017)

"[It is important to use] skilled facilitators which enable all to contribute – the listening of some may need to be encouraged and the speaking by others equally encouraged."
[Elizabeth, Patient and Public Involvement Panel for Antimicrobial Drugs (PPIPAD)]

Figure 2a: The four-dimensional 'cube' depicting a knowledge space (Gibson *et al.*, 2017)
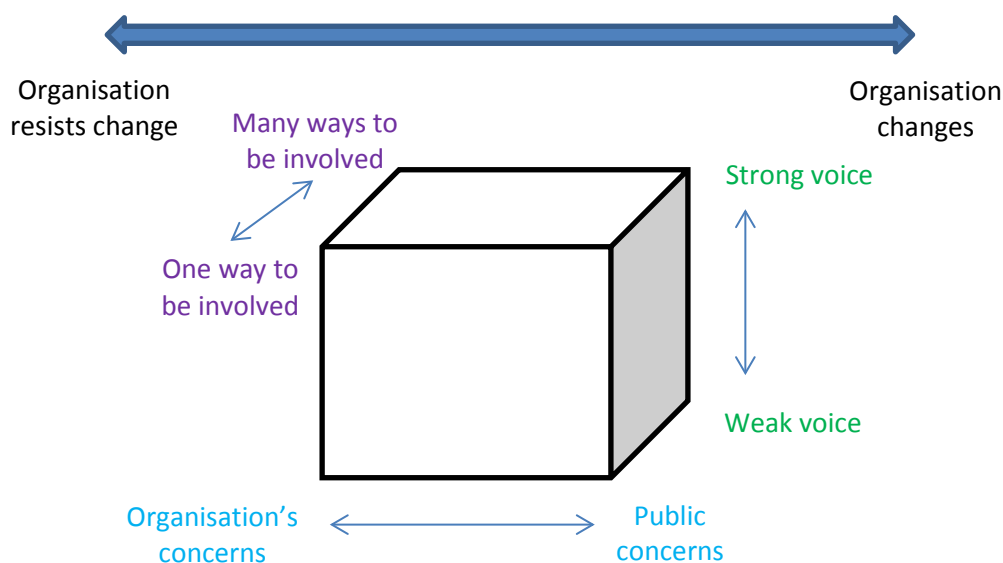
The 'cube' framework above can be used as a planning aid for PPI to help ensure that the relevant issues have been thought about, for example:

- *Weak voice or strong voice.* To what degree are public contributions able to influence decision-making which are acted on, and how are the outcomes of these discussions fed back to them?

- *One way to be involved or many ways to be involved.* Are there different ways that people can contribute to the project, i.e. at different stages of the project or using different methods, such as face-to-face formal meetings, workshops in different locations, Skype, and e-mail, in order to allow people with a wide variety of personal circumstances to be involved?

- *Organisation's concerns or public concerns.* To what degree and in what ways is the research being undertaken able to take into account the needs and concerns of patients and the public, both in its design and conduct, and in its outcomes?

- *Organisation changes or organisation resists change.* Does the wider organisational funding and policy context place limits on what can be changed? Has this been taken into account and made clear?

Developing an approach which addresses these issues can help ensure that conditions are put in place to maximise the potential benefits of PPI. While we are not talking about designing 'perfect' PPI, we are being clear about some of the difficulties and tensions involved in supporting PPI and how we can cope with them. Public contributors are generally aware that there are restrictions in what can be achieved, but they also value honesty and clarity about these issues. This framework can be used again later on to evaluate how well these issues have been addressed and what improvements may be required – this will be discussed in Chapter 10.

2.3   Who to involve

One of the most commonly debated issues in PPI is the 'representativeness' of public contributors, that is who can speak for whom, and on what basis (Barnes *et al.*, 2007, p. 68). The tension is between PPI premised on general representation of an entire public, for example the local community or service users, and one that draws on the knowledge of a select few within it (Martin, 2008). Although it is helpful for researchers to involve a diverse group of people to ensure a wide range of inputs and insights, diversity of experiential knowledge relevant to the specific context is more significant than representativeness in terms of demographics (Staley, 2017). This 'experiential representation', based on shared personal experiences, situations or identity, coupled with active two-way communication, enhance the legitimacy of representation "when economy of time and problems of scale restrict participation" (Martin, 2008).

Public contributors have an equal but different role to researchers in that they add value through their unique perspective of their lived experience (Brett *et al.*, 2012). Both, having direct experience of a particular condition or just bringing a general patient/carer perspective, can be valuable to research (HealthTalk, 2016). In the latter case, input can be valuable if public contributors are able to take a wider view beyond their own experience – some may even find it easier to get involved in a topic that they did not feel so emotional about (ibid).

> *"The skills that a PPI representative has to have is to bring their own experience to whatever the project is and it needn't be anything which is technical, clinical, academic, it can be just their breadth of experience of life, because with that background they will have understandings and insights into issues that can be brought to bear even on something which is clinically very sophisticated." [Anthony, experienced PPI representative; HealthTalk, 2016]*

Figure 2b describes the different sources of lived experience ('experiential expertise') and other additional sources of expertise that may be required for some PPI roles, and can serve as a guide when considering who to involve in research.

Figure 2b: Sources of lived experience or skill of people to be involved (Davies, 2017)

Experiential expertise	1) Having a health or life 'problem'	2) Using health or social care services	3) Having a distinctive perspective
Additional expertise	4) Experience of involvement in research	5) Experience of doing research	6) 'Other' life experience

Finding the appropriate people to involve is challenging, especially for research topics that require involvement of the more general public, people who have had short-term health problems or who only use health services briefly, or those with experience of sensitive and stigmatised issues. Research in antimicrobial medicines development is one example of this. In Chapter 3, we delve deeper into how to create links with patients and the public for PPI in antimicrobial medicines development research.

2.4 When to involve people in the medicines development lifecycle

There are '*unknown* unknowns' that researchers can potentially learn about through PPI at any stage in the antimicrobial medicines development lifecycle, i.e. researchers sometimes "don't know, what they don't know", like when patients point out a flaw in the recruitment strategy that researchers were unaware of (Staley, 2017). There are numerous reports of how PPI has been beneficial to research, but the consistency of its impact cannot be predicted in every case. Therefore, it would be good practice to involve public contributors at every stage of the medicines development lifecycle. While it is acknowledged that the level of contribution may vary from stage to stage, this would at least ensure that researchers do not miss out on any potential learning opportunities that could lead to positive impacts (ibid).

Table 2b provides an overview of when the public can be involved in research and the potential contributions they can make, depending on the potential aim of PPI at that specific stage.

Table 2b: Potential PPI aims and contributions in research (Davies, 2016)

Stage of research	Potential PPI aims	Potential PPI contributions
Research design and planning	To ensure the right research is being done	Prioritisation of research topics that are important to the public
	To ensure research benefits the public	Ensure: - research questions address issues of importance to the public - research generates knowledge that could improve health, treatment or care - research measures and/or values outcomes and findings that are important to the public
	To ensure research is acceptable to potential participants	Ensure: - research methods are reasonable, ethical and practical - treatments, procedures or other interventions given or withheld are reasonable and ethical - benefits and risks to participants are reasonable, ethical and communicated clearly
	To ensure researchers communicate well with participants	Ensure plain English summary, patient information and research instruments are accessible, and easy to read and fill in
	To help researchers secure funding and get approval for research	Write letters of support and approval of researcher plans
	To ensure appropriate plans for involvement are in place	Ensure plans for PPI in conduct of research and dissemination of findings are robust, clear and resourced appropriately
Conduct of research	To ensure research is acceptable to potential participants	Ensure: - treatments, procedures or other interventions given or withheld are timely and delivered with sensitivity

		- benefits and risks to participants are reasonable and ethical
	To ensure researchers communicate well with participants	Ensure: - information provision and collection are appropriate and timely - verbal communication in recruitment and data collection is clear, uses simple words and language; advise on and pilot these processes - documents are clear, of appropriate length, and easy to read and fill in
	To support recruitment and retention	Advise on: - where, when and how to approach potential participants - retention strategies and how best to keep in touch with participants; ensure participants receive updates on the progress of research
	To support data collection	- Advise on when and where to collect data - Pilot interviews and questionnaire completion; consider question order, clarity, time taken, and other practicalities - Help with data collection in some studies
	To support data analysis	- Provide patient, service user, carer perspectives on qualitative coding, themes, and/or appropriate names of themes - Conduct data analysis alongside researchers in some studies
Dissemination	To identify findings of interest to the public	Review findings to identify those of most interest/benefit
	To encourage communication of research findings to non-academic audiences	Advise on communication of findings to: - participants - patient and service user/carer groups and organisations and to health professionals
	To contribute to academic reporting of research and findings	Feedback and/or co-author journal articles and research reports
	To support presentation and sharing of findings	Attend conferences, events and meetings to support dissemination
	To encourage implementation of research findings	Encourage researchers to consider how the findings might improve treatment and care
	To encourage reporting of involvement	Co-author publications reporting involvement processes and impact of involvement

With proper planning, training and support of researchers and public contributors, it may be possible to implement most of these aims and contributions in antimicrobial-related research. The role of PPI at various stages of the antimicrobial medicines development lifecycle is explored further in Chapters 5 to 8, including a consideration of potential contributions to research agenda setting, medicines discovery, clinical trials, and regulatory processes.

TIP BOX 1: HOW TO... have effective PPI. (Cossar and Neil, 2015)
- Establish clarity about the role of public contributors.
- Have several public contributors with diverse and relevant experiences, who will develop confidence as a cohesive group over the course of the research project.
- Work in an inclusive manner, focusing on processes and building trust relationships.
- Provide practical and emotional support to public contributors.
- Break down the research into manageable tasks.
- Communicate and feedback regularly to public contributors about their impact on the research between meetings.
- Be willing to learn and committed to overcoming challenges.
- A commitment to PPI on the part of research funders.

KEY POINTS
- PPI is not an intervention, but rather a conversation or knowledge space, where researchers and the public exchange ideas, values, assumptions and experiences.
- Researchers should consider involving a group of public contributors that is diverse in terms of experiential knowledge that is most relevant to the context of the project.
- PPI should happen at every stage of the antimicrobial medicines development lifecycle as there is potential for learning to lead to positive impacts throughout the lifecycle.

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3   Creating links with patients and the public

ABSTRACT

Finding and supporting patients and the public to contribute unique insight and perspectives are key to effective PPI in research. This chapter deals with the opportunities and challenges in looking for people to be involved in antimicrobial medicines development research (not to be confused with recruiting participants for clinical trials). We describe three key considerations: who you want to involve, what you want them for, and what time commitment you require from them. We discuss the various strategies for seeking people with different perspectives for antimicrobial research (summarised in Tip Box 2).

Two appendices are mentioned in this chapter: a template expression of interest form (Appendix 2), and a template letter to responders who are not selected for a PPI panel (Appendix 3). Input from members of the Patient and Public Involvement Panel for Antimicrobial Drugs (PPIPAD) were particularly important in informing the development of this chapter, and many of their contributions have been included as quotations. We conclude by considering the ethics and consent processes for PPI in research.

3.1   Finding the appropriate people to involve

For PPI to be effective, researchers need to look for individuals who will be able to contribute unique knowledge and perspectives. Researchers should establish clear criteria before setting out to find public contributors, and consider what support they would be able to offer to those they plan to involve. INVOLVE suggests preparing a brief 'person specification' (see '*Who do you want to involve?*' below) and 'role description' to guide the selection process, but also emphasises the importance of being flexible.

The following questions should be considered when deciding on the people to involve (Hardavella *et al.*, 2015):

- *Who do you want to involve*? For example, do you want people with direct or indirect (carer) experience of a specific infection; does the infection experienced need to be serious to the point of hospitalisation; would you involve people who have or do not have previous experience of research involvement?

- *What do you want them for*? For example, what role or activities are you expecting to involve them in; what level of involvement is required? (Table 3a)

- *What time commitment do you expect from them*? For example, how often do you plan to meet; how long are meetings likely to run for; when is the expected end date for their involvement?

Table 3a: Three different levels of involvement (WEAHSN, 2016)

The individual	Small groups	Broader engagement activities
- Shared decision-making and self-care - Participant in a research project - Helping to co-design services - Acting as observers - Giving individual feedback	- Advisory groups, steering groups, governance bodies - Discussion groups or workshops	- Events - Communicating with former or current patients of acute services - Using social media

Depending on the role of the public contributor, the WEAHSN (2016) recommends a maximum length of involvement of two years, not only "to allow for fresh skills and new perspectives to be introduced" into the PPI panel, but also to offer opportunity to those whose personal circumstances no longer support involvement in research to withdraw. Any new public contributors will require appropriate training and it may take time to build a good working relationship with them.

In considering how many public contributors to involve, a reasonable number would be able to effectively generate discussion, and confidently hold their position among the academics and health professionals within the research team, to challenge and influence their opinions when required. Thus, it would seem practical to involve at least two people, but no more than twelve, to ensure everyone is able to contribute effectively. Involving more people would increase the breadth of experience, views and skills brought to research. This would allow different people to be involved in different projects, at different stages, and in various roles – but remains subject to project-specific needs (INVOLVE, 2012; HealthTalk, n.d.). For example, if a project requires lay representatives to be involved in research advisory groups or steering groups, then two or three people will suffice; whereas workshops to identify and prioritise research topics will probably require between nine to twelve people to generate ideas and discussion. Other advantages of involving more than one person are it provides opportunities for peer support and encouragement, and ensures a public perspective is maintained in the event of drop out or poor attendance (INVOLVE, 2012).

3.1.1 Strategies for seeking people to involve

Different approaches can be used to look for people with varied perspectives needed for antimicrobial research. Local hospital research departments or organisations that promote PPI in research, and who have close links with other health and academic organisations, may be able to advise on how to find and make contact with the people who you want to involve. Examples of organisations with good links are the UK's Research Design Service (RDS) and Clinical Research Network (CRN), and the European Patients' Academy on Therapeutic Innovation (EUPATI). Some strategies for finding public contributors are described in Tip Box 2.

The next step will be to invite all those who have responded to an initial meeting, where they will receive more information about the research that they may potentially be involved in – cost for this initial meeting would include room hire and provision of refreshments, but not reimbursement of travel expenses. Selecting the right conditions will be key to enabling as many people as possible to attend this meeting and subsequent meetings – scheduling an approximately two-hour meeting to be held in the early evening will enable them to go along after work and help them to remain engaged for its entire duration. Creating a supportive environment where people can meet the research team and ask as many questions as they feel necessary without any obligation to continue being involved will be important, as some may find it difficult when traumatic memories resurface while talking about past experiences (Grier *et al.*, 2018).

> **? TIP BOX 2: HOW TO… find public contributors for antimicrobial research. (INVOLVE, n.d.; Hardavella *et al.*, 2015)**
>
> - Consult community members or patients, and other healthcare professionals such as practice managers, how best to find people who might be interested in getting involved.
>
> - Advertise the involvement opportunity in places like clinics, local newspapers, and/or online social media platforms.
>
> - Search online for relevant organisations that promote PPI in research who could include details of the involvement opportunity on their website or newsletter, e.g. People in Research.
>
> - In the UK, you may consider contacting stakeholders who represent the communities served by the local hospital, e.g. NHS Trust members or its Patient Advisory Liaison Officer.
>
> - Coincide the campaign to find public contributors with events that would be attended by people that would potentially fit the inclusion criteria for the panel: include flyers (colourful, illustrative, attractive) advertising the opportunity inside delegates' information packs.
>
> - Directly approach patients who attend a relevant clinic, or who are known personally to fulfil the inclusion criteria and may be interested and willing to be involved.
>
> - If applicable and necessary, extend an invitation to members of a previous project-specific panel to re-collaborate on the new panel.

Another crucial aspect of this initial meeting is to make clear that the purpose of finding people is for the opportunity to work in partnership with the research team in a way that is different to being a research subject or participant – misunderstandings about this tend to occur despite efforts to make the intention clear – the 'role description' document will be very useful for this purpose (ibid). It is also important to be clear about the expected length of involvement:

> *"I think it is [important to be clear how long involvement is going to last for], whether it's going to be six months or whether it's two years, you know, just to get some idea. You can never perhaps be sure as to what it's going to be, but at least it gives you some idea as to what your commitment might be."* [David R., PPIPAD]

Responders can be required to complete a short expression of interest form (see Appendix 2 for template), to facilitate the research team in forming as diverse a group as possible. Those unable to attend the initial meeting should be sent all the key information and given a reasonable deadline for the return of forms (e.g. two weeks), after which the research team can convene and discuss panel selection. A template letter to inform responders who are not selected for the panel is available in Appendix 3.

3.1.2 Challenges

Finding the right people for PPI may be more challenging and time-consuming than anticipated, especially in an acute care and laboratory-based field such as infectious disease and microbiology, where PPI is relatively unheard of (Evans *et al.*, 2017; Hardavella *et al.*, 2015). Therefore, INVOLVE (n.d.) advises to allow plenty of time to make contact with organisations and individuals. The process needs to be led by a research team member who is committed to the cause, willing to take ownership, and who will keep the team motivated despite any early setbacks (Grier *et al.*, 2018). However, the

commitment and determination of the whole team will be key to successful establishment of a PPI panel (ibid).

The area of acute infectious disease does not have established patient support groups or voluntary organisations. Patients who have experience of non-threatening infections do not usually require ongoing or regular contact with health services as a direct result of the infection, therefore, they are less likely to have a strong interest for or to actively seek involvement in antimicrobial research. Conversely, if the infection is serious and requires hospitalisation, patients would be too unwell to participate in research anyway, and if they recover, they may not remember their experience in an intensive care unit, or they and their families may refuse involvement due to the trauma of the experience (Grier *et al.*, 2018). However, if successfully selected, those who have been hospitalised due to a serious infection will be best placed to comment on research that might involve patients who are very ill and perhaps unable to provide consent for themselves (ibid).

Ensuring the representativeness of a PPI panel, such as involving seldom heard ethnic or social class groups, is a well-recognised issue and one that is not easy to address with limited resources. People who end up being chosen for the panel may be self-selected – they may have responded to the opportunity for involvement with a pre-existing interest in research, thus may hold a particular bias, and their views may not necessarily be representative of the wider population (HealthTalk, n.d.; Grier *et al.*, 2018). Nevertheless, they may be less inhibited to voice their opinions and contradict researchers in the interest of other patients (ibid). There is also a risk of people responding out of interest in the payment they will receive for their involvement, rather than a genuine desire to contribute to research (HealthTalk, n.d.).

> *"We know that there's actually a variety of practical and cultural reasons why some sections of the community get involved more than others. Spending time worrying about representativeness, I think, just misses the point that what we want is to make sure that we've got patient and public views alongside professional views. Obviously, one wants to be open to encouraging maximum diversity, but the reality is we're not going to get it, so it's better to get a group like this, really active, and value the contributions that this group gives, rather than worrying too much about the people who aren't here." [David E., Professor in Health Services Research]*

Resource budgeting for PPI in research is another challenging aspect that needs to be accounted for at the earliest stage possible (Mental Health Research Network and INVOLVE, 2013). A significant amount of time will need to be invested in preparing for PPI, which may include time to obtain relevant training.

> *"I think you might say, at some point, that the general panels like this one, are likely to be more difficult and therefore, more expensive to recruit than a simple disease-based panel, where you've got a relatively simple selection criteria and selection method. The more general you become, the more expensive it's likely to be as part of the budget for the whole project." [Richard C., PPIPAD]*

> *"I haven't got any experience of recruiting a panel at all, let alone a panel like this. But we got a lot of advice before we started, and although that took a long time, we thought out a lot of stuff before we started, and I think, if you don't do that, you're going to waste a lot more time and a lot more money." [Sally, PPI Coordinator]*

As already mentioned, finding the right people for PPI is a time intensive process. Then there are financial costs to consider, which include printing, room hire, catering, and reimbursement of expenses for attending meetings subsequent to the initial meeting (Grier *et al.*, 2018). In the long run, the challenge would be to secure funding for sustainability of the group of people selected (HealthTalk, n.d.).

3.1.3   Facilitating strategies

When seeking for people to involve in antimicrobial research, it is more significant to ensure diversity in terms of experiential knowledge that is most relevant to the context of the project, than to aim to be representative of the population i.e. demographics (Staley, 2017). Higher response rates may require personal contact with the research team rather than wider advertising efforts (Grier *et al.*, 2018). It may also be easier to gain expressions of interest from people who have some link to your organisation, and therefore some vested interest, such as hospital members, i.e. former or current patients of acute services (ibid). Preference for the direct and personal approach was affirmed by members of PPIPAD, who themselves were mostly sought through a personal email, letter, or face-to-face invitation.

> *"I think the direct approach is the right one, because you can get flyers, you can see notices and think, "oh, that might be interesting" and don't do anything about it; whereas if you got a direct request, I think it does make a difference." [David R., PPIPAD]*

> *"Unless you're somebody who's actively looking for something to participate in, you're probably not going to respond [to less direct approaches]." [Sally, PPI coordinator]*

PPIPAD members also shared their opinions on when they thought was the best time to contact people who might be interested in the involvement opportunity:

> *"I would have thought the closer to the event, then the more likely you are to get a positive response. Even if someone is still receiving treatment, they're likely to respond more than someone who had it 10 years ago and has more or less forgotten about it." [Richard C., PPIPAD]*

> *"One would say up to about six months after [the patient] has been discharged from the hospital, because when you're closer [to the event], you're busy. I'm talking as a carer trying to sort out life… that we had a reasonable time." [John, PPIPAD]*

PPIPAD provided some insight into what might motivate people to get involved in antimicrobial research by sharing their own motivations for getting involved – these mainly related to concerns with the impact of antimicrobial resistance (AMR) in wider society, a sense of wanting to give something back, and feeling as if they had something to offer (Grier *et al.*, 2018):

> *"Antibiotics have played a huge part in my recovery and continuing health. Any kind of research to help improve antibiotics is of paramount importance to the future." [Judith, PPIPAD]*

"I believe I could make a useful contribution and am interested in the issues involved. Also, now that I am in the third age and have free time I would like to use it constructively." [Neil, formerly of PPIPAD]

"[I am] concerned about antibiotic resistance and interested in ethical issues in medicine, particularly in connection with commercial involvement in drug development." [Richard C., PPIPAD]

"Interested in the subject and keen to give something back. Also to make research more relevant to patients." [Elizabeth, PPIPAD]

The use of a short expression of interest form is helpful for prompting people to reflect on their motivations for involvement, and support a sense of value and commitment to research (see Appendix 2 for template).

INVOLVE and members of the Public Involvement Collaboration Group have produced a '[tips sheet](#)' that offers some practical advice on seeking members of the public for involvement in research processes. Ultimately, selection for PPI in research should aim to go beyond being project-specific, to form a sustainable 'community of practice' in which knowledge, skills and experiences continue to be shared and developed, and who can be called on for different roles in different projects – this group would require structured organisational support to help maintain it (HealthTalk, n.d.; WEAHSN, 2016).

3.2   Ethics and consent

Involving patients and the public in the design and development of research does not generally raise any ethical concerns, since they will not be acting in the same way as research subjects or participants. Hence, ethical approval is not required for researchers to involve people in, for example, research advisory groups, helping to develop a protocol, questionnaire or information sheet, or preparing a funding application. However, there are some situations where PPI may raise ethical concerns, for example:

- When individuals involved are susceptible to a specific risk, or are considered 'vulnerable' such as people with dementia or children – in these cases, governance should be in place and consent sought from the parents or carers (NIHR, 2016)

- When individuals will be involved with collecting and analysing data, such as helping to conduct interviews, facilitate focus groups, recruit research participants, or analyse survey data – in these situations, the following ethical issues should be fully addressed in the application to research ethics committees:

   a) The wellbeing and safety of the *people who are actively involved as researchers*. They may find that looking at and discussing the data, or talking to other people with similar experiences of serious infections remind them of their own traumatic experiences. Therefore, additional counselling/support must be available to any individual who is distressed when carrying out the research.

   b) The wellbeing, safety and preferences of the *people who are taking part in the research as study participants*. These people must not be exposed to any additional risks or concerns. Other issues or sensitivities that may arise for study participants must be considered, for

example, some patients may be less comfortable being recruited by other patients compared to healthcare professionals.

c) In consideration of the wellbeing and safety of both, the *people involved as researchers* <u>and</u> *those taking part as study participants*, any member of the public carrying out the research must have adequate training, support and supervision appropriate and proportionate to the circumstances, in the same way as any other member of the research team – this may or may not include training in confidentiality, and giving and withdrawing consent. The proposed involvement, including any direct contact with study participants, must be appropriate. (HRA/INVOLVE, 2016)

One particular issue that pharmaceutical companies are often concerned about is the perceived legal or regulatory restrictions around involving patients as partners in medicines development research. This concern may be alleviated through the inclusion of confidentiality clauses within consulting agreements – this issue is addressed again in Chapter 7, as one of the potential challenges of PPI in clinical trials.

KEY POINTS

➢ The search for public contributors should consider who you want to involve, what you want them for, and what time commitment you require from them.

➢ At least two and up to twelve members of the public may be involved, depending on the role or activity they will be involved in.

➢ Various strategies can be used to look for different people with different perspectives needed for antimicrobial research. All those who respond are invited to an initial meeting to receive more information, ask questions, and complete a short expression of interest form.

➢ Challenges of seeking public contributors: requires a lot of time, commitment and determination; no established patient support groups or voluntary organisations in the area of acute infectious disease; high chance of self-selection; difficult to secure funding to sustain the PPI group.

➢ Facilitating strategies: personal contact with people who have experience of acute infections, especially those who are concerned with the impact of antimicrobial resistance in wider society, have a sense of wanting to give something back, and feel like they have something to offer.

➢ PPI in research does not require ethical approval <u>unless</u> the members of the public involved will be collecting and analysing data. Confidentiality clauses can be included in consulting agreements between pharmaceutical companies and public contributors to alleviate any concerns about legal or regulatory restrictions.

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4   Planning and preparing for PPI

ABSTRACT

After successfully selecting people to be involved in antimicrobial medicines development research, there are several aspects to consider in planning and preparing for PPI. This chapter makes recommendations for strategic planning of organisational responsibilities (summarised in Tip Box 3), costs and payments, training and support, accessibility, meetings, and documentation. These are largely based on guidance by the National Institute for Health Research (NIHR) INVOLVE Advisory Group and from our extensive experience of implementing PPI in the western region of England.

We have included links to various online resources, namely an example of a 'terms of reference' document for a PPI panel, an Involvement Cost Calculator, and practical advice on budgeting for PPI. There are also links to several organisations that provide PPI training for researchers and public contributors. Key inputs from members of the Patient and Public Involvement Panel for Antimicrobial Drugs (PPIPAD) have been quoted, particularly in the sections relating to training and support, and meetings.

4.1   Strategic planning – organisational responsibilities

Make early contact with the relevant departments within your organisation, such as finance and research departments, to inform them about the proposed arrangements for PPI. This allows time to address any concerns raised by these departments and is important to ensure the smooth implementation of PPI activities within research. Issues that might need to be considered include:

- payment and expenses policies
- travel and expenses claim forms
- methods for paying people (including tax deductions)
- health and safety
- insurance and indemnity
- confidentiality agreements – **all** members of the research group should be required to sign a confidentiality statement, not just the public contributors (INVOLVE, 2012)

Plan timelines and include these in a Gantt chart to guide the organisation and implementation of PPI activities within the research.

TIP BOX 3: HOW TO... have clear organisational responsibilities concerning PPI. (INVOLVE, 2012)

- Appoint an experienced and adequately resourced member of the research team to be the PPI lead, so there is a point of contact for all involved.

- Develop terms of reference and/or a role description for the PPI panel.

- Make sure that public contributors understand that they can withdraw involvement at any time.

- Identify appropriate facilities or put professionals in place that can provide emotional support to those who may find the process of involvement distressing in terms of the information discussed – if applicable, this should have already been addressed when applying to the research ethics committee (see Chapter 3.2).

- Where appropriate, discuss in advance what will happen should people become ill for periods of the research, or decide to withdraw from the panel.

- Devise a maintenance plan for PPI to enable public contributors to continue using the skills they have developed after completion of the current research project, for example signposting to opportunities for involvement in further research.

4.2   Costs and payments

Plan and prepare a budget for PPI at the earliest stage possible. Some funders, like the NIHR, require PPI costs to be built into research grant applications. The Involvement Cost Calculator is useful for this purpose. Depending on who is being involved and how, the costs shown in Figure 4a might need to be taken into consideration. In general, it is good practice to offer payment to public contributors whenever possible. Fees and expenses that have been agreed upon should be paid promptly. More practical advice on budgeting for PPI in research is provided by INVOLVE.

Figure 4a: PPI costs to be considered (INVOLVE, 2012)

Training and support	Travel and subsistence expenses	Childcare and carer costs	Payment for time and work undertaken
Venue hire	Refreshment costs	Translation and interpretation costs	Administrative support
Telephone, photocopying and postage	Additional support, e.g. independent facilitator	Attendance at conferences and events	Writing publications and journal articles

4.3　Training and support

Training and support may be required for the researchers, as well as the public contributors. The type of training and support will depend on the research project, the role of the public contributors, and the needs of individuals. These needs may change as a project progresses and people become aware of the skills required for effective PPI.

4.3.1　Training

- General training on topics such as:
  - o Building research partnerships with the public
  - o Group facilitation skills

  These are flexible and less intensive sessions, useful for, and can be opened to, a joint audience of researchers and public contributors. Such workshops are organised by the People in Health West of England (PHWE) to help people develop understanding, skills and confidence for innovative and effective PPI in research.

- Specialised training:

  - o Training courses can be designed specifically for public contributors to provide them with information about antimicrobial resistance, the issues around antimicrobial medicines development, clinical trials, and other related topics. The EUPATI Expert Training Course is one such avenue for patients to receive intensive training in medicines research and development, although to date, none of the graduates since the course first started in October 2014 have specific expertise in acute infectious diseases.

  - o The Australia-based consumer and community health research network, Involving People in Research, offers a one-day training workshop that focuses specifically on the needs of laboratory-based researchers who want to incorporate PPI into their research.

- 'On the job' training

- Training through sharing knowledge and experiences with colleagues and peers, for example a researcher may explain his/her work to colleagues and invite them to comment on certain aspects of it (INVOLVE, 2012).

  "I think that [training] is more important in a general panel like this is. Whereas if you're dealing with a disease-specific panel, they're likely to know much more about the problems involved. In a general thing such as we're on now, you might well need quite a lot of "education" to start with." [Richard C., PPIPAD]

4.3.2　Support

Researchers or managers responsible for PPI can be supported through team meetings or one-to-one meetings with line managers, or by having a mentor with experience in PPI, where this is available (INVOLVE, 2012), perhaps via the COMBACTE consortia. Both, researchers and public contributors can benefit from formal or informal mechanisms of peer support (ibid). Some organisations may offer support to public contributors through:

- advice and guidance
- access to training

- mentoring
- networking opportunities
- resources and information (Involving People in Research, 2017)

Researchers, particularly senior investigators, who regularly attend and actively participate in panel discussions, demonstrate commitment, which has a positive effect on public contributors in that they feel that their involvement is being valued.

> *"I think at one point we were actually outnumbered by the [professional] staff that were here, which was great because that showed their commitment to do it in the first place and get the thing off to a good start." [David R., PPIPAD]*

This kind of direct interaction between lead/senior researchers and public contributors may also increase the chances of PPI having a positive impact on the research. Nevertheless, there may be concern that in some situations where public contributors are outnumbered by the researchers, the former may feel too overwhelmed to effectively contribute. The PPI lead will need to be sensitive to the needs of the people and make necessary adjustments.

4.4 Accessibility

Considerations of appropriate communication methods, and accessibility of meeting venue and time, should ideally be considered in parallel with the type of people that researchers want to involve as public contributors.

4.4.1 Communication

- Ensure style of written and verbal communication is friendly, simple and clear, avoiding jargon.
- Check preferences for postal or email communications – do not assume that everyone would have easy access to a computer or be able to print out long documents.
- Find out how specific accessibility needs can be met, for example people with visual or hearing impairments, learning difficulties, chronic long-term conditions, or non-native language speakers (pan-European meetings may need to be interpreted into multiple languages).
- Provide information about meetings (timings and directions to the venue) and any preparatory reading well in advance and in a relevant format.

4.4.2 Meetings

- Venue:
  - Easy for people to get to – has parking and public transport nearby.
  - Reasonable cost of travel to the venue, in terms of mileage and public transport fares.
  - On neutral ground – would not be associated with difficult experiences; for example, using a community venue instead of a hospital meeting room.
  - Accessible to people who use a wheelchair, have mobility problems, or other disability.
  - Essential equipment available, such as a projector or microphones.
  - If some of the meeting members are unable to attend in person but can meet virtually, for example via Skype, or via telephone conference meetings, then the venue should have the necessary capabilities to facilitate this.
  - If appropriate, consider other alternatives to face-to-face meetings such as online forums.

- Time:
  - Lunchtime meetings might suit those who are not working.
  - Breakfast meetings, or late afternoon/early evening meetings (outside of office hours) might suit groups where some people are working, have young children or who are carers – venue hire during these times may also cost less.

4.5   Meetings

Meetings are a common feature of PPI in research. It is important to plan and conduct these meetings well as they can have a big influence on how public contributors feel about the research and the extent to which they are able and want to get involved.

4.5.1   Planning for meetings

The following recommendations are in addition to the ones on accessibility (venue, time and communication) mentioned in Chapter 4.4:

- Plan and prepare a budget for your meeting.

- Plan topics over a series of meetings to benefit both researchers and public contributors.

- Plan meetings to last for a reasonable length of time, e.g. no longer than two hours, including a break midway through.

- Plan intervals throughout a presentation to allow discussion to develop, and to ensure that public contributors are not 'left behind'.

- When planning refreshments, ask people if they have any special dietary requirements.

- Where necessary, arrange to have microphones and hearing loops for people with hearing impairments, large print for people with visual impairments, interpreters for non-native language speakers, or for sign language.

- Key people like the PPI lead and principal investigator should have a pre-meeting or telephone discussion to agree on meeting objectives and to plan an agenda, including timings for discussions and presentations.

- Whilst a clinical trial is in progress, you may plan meetings with public contributors to occur less frequently or as necessary, but it is important to maintain communication and keep them informed.

4.5.2   Conducting the meetings

- Create a safe and supportive environment where public contributors feel welcomed, included, and able to make comments and share ideas, for example by introducing everyone using first names, for both professionals and public members.

  "You want an environment where everyone feels comfortable to actually participate. Don't put people down in meetings. [A] friendly atmosphere [helps me participate]." [Roy, PPIPAD]

  "Some professionals do introduce themselves as Doctor [so and so] and actually, that immediately sets up an inequality if the professionals are using their status and patients

don't have the same status. So I think first names do [help to] equalise the conversations." [David E., Professor in Health Services Research]

- Consider providing public contributors with an information sheet that includes a small photo and brief description of who the professionals in the meeting are.

- Conduct administration as people arrive, such as asking public contributors to sign for receipt of travel and attendance expenses.

- Provide name badges or desk labels in a large clear text font, and ask people to introduce themselves at the beginning of the meeting.

  "I was confused as to who were panel members and who were the professionals. One really good thing is if you could just do a quick note about the professionals that were going to be there. Perhaps a mugshot and a sentence as to what they do or why they're here. Because some of you are from the university, some from the hospital, it's really useful from our point of view, to know who is from where and what they're about." [David R., PPIPAD]

  "Have a little name label, just stick it on the desk if you're here. You know, a bit of card, folded over, and in block capitals so short-sighted people and long-sighted people can actually read it." [Lesley, PPIPAD]

- Ensure even distribution in sitting arrangement, i.e. professionals and public contributors should sit among each other, and not in separate groups.

  "Professionals could purposely not sit in a row at the front. Sit amongst the [public contributors]. It's something the organisers can do, which the other members of the panel might not feel able to do. The organisers can distribute themselves." [Richard C., PPIPAD]

- Assign a member of the research team to take notes, ideally someone who is not involved in facilitating group discussion. If the meeting needs to be audio-recorded, ask the group for permission to do this.

- Agree ground rules for how meetings will be conducted to foster mutual respect and ensure everyone has an equal opportunity to contribute.

- Encourage the use of clear and simple language, avoid jargon and explain acronyms; the lead facilitator should regularly check that the content of the meeting is understood.

- Have sufficient breaks and refreshments not only because people might need to take medication or find sitting for long periods difficult, but also to keep them engaged with discussions.

- Depending on the size of the group and purpose of the meeting, it might be necessary to break off into smaller groups to give everyone the opportunity to contribute to the discussion.

- Whenever possible, start meetings on time or try not to delay for too long before starting. End the meetings at the time advertised.

4.5.3   After the meetings

- Write up and distribute notes taken during the meeting, along with any action points, to all public contributors (not just those who attended the meeting).

- Provide feedback to public contributors on any recommendations or outcomes that arose out of the meeting.

- Request for feedback and any suggestions for improvement for future meetings.

- Offer the opportunity for any additional and relevant comments to be sent in after the meetings.

"If we asked a question and the answer was a lot bigger than we had the time for, you actually did not ignore it, you came back the next meeting and said, "This is what you asked for and this is now what we're going to spend the first 15 minutes on to give you some background on that." Nothing got lost." [David R., PPIPAD]

"If we'd not been able to attend a meeting, it's always been good that we could catch up on the literature. It's always been emailed to us or something. So, although I've been abroad, I've still not missed out on the notes, and that's important." [Lesley, PPIPAD]

4.6   Documentation

Any personal data about public contributors collected by researchers must be stored securely in accordance with the organisation's data protection policies, and made accessible only to authorised members of the research team. Consider how to keep a record of the various PPI activities carried out during the course of the research, as well as their outcomes. This will be helpful for evaluating the impact of PPI and subsequent reporting to research funders and public contributors. See Table 10b in Chapter 10 for an example of a simple impact log for recording the outcomes of PPI in research (template available in Appendix 4).

KEY POINTS

Planning and preparing for PPI requires consideration of the following:

➢ Strategic planning of organisational responsibilities for effective and efficient implementation of PPI activities

➢ Costs and payments of expenses to public contributors

➢ Training and support for researchers and public contributors

➢ Accessibility – communication format and methods, as well as meeting venue and time

➢ Meetings – planning, conducting and feedback afterwards

➢ Documentation of PPI activities for impact evaluation and reporting

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5 PPI in setting the research agenda

ABSTRACT

The research agenda in medicines development has traditionally been established without PPI. In other areas, professionals and patients are thought to have different research priorities, presenting productive differences in setting the research agenda. Such differences, however, may not be as apparent in antimicrobial medicines development, since the common need is for the most effective antibiotics with the least side effects. Nevertheless, PPI in research agenda setting is vital and necessary in response to patients' needs, suggesting new avenues of research, to ensure a democratic process, and to improve acceptance of decisions and outcomes.

This chapter describes two approaches that can be used to structure the process of collaboration between patients and professionals in setting the research agenda: the Dialogue Model and the James Lind Alliance Priority Setting Partnerships. We present key points raised by the Patient and Public Involvement Panel for Antimicrobial Drugs (PPIPAD) in our critical analysis of both approaches. As a result of discussions with PPIPAD, we propose a simpler and possibly quicker alternative approach to involving patients in research agenda setting.

5.1   Introduction

Topics for research in healthcare (health research agendas) have traditionally been established without PPI – the same applies to medicines development, including antimicrobials. For example, to address the most crucial current knowledge gaps around antimicrobial resistance, the World Health Organization (WHO) published a list of priority research topics that was constructed entirely by a group of experts (WHO, n.d.). One of the key findings from the 2013 Report *Priority Medicines for Europe and the World* was the need for further development of the role of patients and the public in contributing to priority setting, and to regulatory and pricing decisions (Kaplan *et al.*, 2013).

Lowe *et al.* (2016) interviewed several healthcare thought leaders from the pharmaceutical industry who were able to cite present examples of PPI in medicines development – including informing product strategy and clinical trial design – but stated that these were exceptions, and that PPI needs to be embedded into practice and incorporated consistently within and across companies. Lowe *et al.* (2016) also interviewed patient thought leaders who emphasised the need for patients to be involved from the start: *"Patients should be engaged early and often and there is a place at each step from conception all the way to [FDA] approval"*.

Different research priorities between professionals (i.e. academics, clinicians) and patients present challenging perspectives and issues in setting the research agenda. Topics that are only considered important by professionals may be seen as irrelevant to patients or not meeting patients' needs. Conversely, if topics are only considered important by patients, there is a risk that professionals will not submit research proposals on these topics. However, such differences may not be as apparent in antimicrobial medicines development – professionals, patients and the general public all want the most effective antibiotics with the least side effects. Even issues such as easier modes of antibiotic delivery (i.e. oral versus intravenous injection), may be important not only to patients but also to clinicians and pharmaceutical companies, albeit for different reasons.

Nevertheless, it is vital that professionals and patients work together in partnership to discuss any differences – a mutual understanding of the technical aspects of medicines development that cannot be altered, such as the delivery mechanism of a medication or regulator-established clinical trial endpoints, and why these cannot be altered, is essential for a meaningful engagement process (Lowe *et al.*, 2016). Involving patients in research agenda setting, is not only addressing the need to be more responsive to patients' needs, it also ensures a democratic process, and can improve acceptance of the resulting decisions and outcomes (Elberse *et al.*, 2012a).

Case Example 5a: A better understanding of patient needs to inform medicines development and prevent costly missteps (Lowe *et al.*, 2016; Mack, 2007)

The inhaled powder insulin product, Exubera, was approved by the US Food and Drug Administration (FDA) in January 2006 for use as a mealtime insulin, but the makers of the product withdrew it from the market in October 2007. This novel product took 11 years to develop and was meant to offer the convenience of an alternative, less invasive route of administration over injected insulin. Unfortunately, the delivery device – about the size of a torch – was found to be too cumbersome and patients did not find it appealing enough to stop using injectable insulin. As a result of the failure to gain the interest and acceptance of both, patients and healthcare providers, Pfizer made the decision to voluntarily withdraw Exubera, despite there being no safety or efficacy issues. The decision cost the company $2.8 billion.

5.2   Mechanisms for involving patients in research agenda setting

This section describes two common approaches used to structure the process of collaboration between patients and professionals in setting the research agenda.

5.2.1   The Dialogue Model

This model was developed on the notion that involvement is an interactive process between stakeholders (Abma and Broerse, 2010). Patients and professionals are seen as having unique and relevant perspectives, and dialogue will result in shared understanding and agendas. The model has been validated in seven research agenda setting projects among various diseases and patient populations: spinal cord injury, neuromuscular diseases, renal failure, asthma/chronic obstructive pulmonary disease (COPD), burns, diabetes, and intellectual disabilities (ibid). Table 5a describes the six phases of the Dialogue Model.

Table 5a: The Dialogue Model (Abma and Broerse, 2010; Elberse *et al.*, 2012b)

Phase	Aim(s)	Methods
1. Exploration	To create good social conditions for the dialogue process (i.e. openness, respect, trust, commitment, etc.) To gain a first understanding of the stakeholder issues	• Establish project team • Identify key stakeholders, i.e. patient and professional groups • Draw up an initial list of issues, perspectives, and ideas • Create the social conditions for collaboration

2. Consultation	To identify the research agendas of different stakeholder groups	• Consult different groups separately – consider various methods to meet the different needs of a diverse population • Analyse and integrate data, then feedback to participants to check interpretation
3. Prioritisation	To prioritise each stakeholder group's research topics	• Questionnaires (involve patients in the design and analysis) • Interviews/focus groups to support analysis of questionnaire outcomes • Delphi technique (i.e. repeated written responses; Figure 5a), for relatively small stakeholder groups
4. Integration	To integrate the agendas via a fair and meaningful negotiation process	A dialogue meeting with stakeholder group representatives
5. Programming	To develop a programme based on the integral research agenda To maintain stakeholder engagement	Various possible methods depending on the research question(s), e.g. quantitative methods to evaluate effectiveness of a treatment; qualitative methods to assess effectiveness of communication
6. Implementation	To implement the research programme	• Respond to calls for proposals by research funders • Match research themes with research groups • Stimulate research networks

Figure 5a: Representative scheme of the Delphi technique (adapted from Pereira and Alvim, 2015)
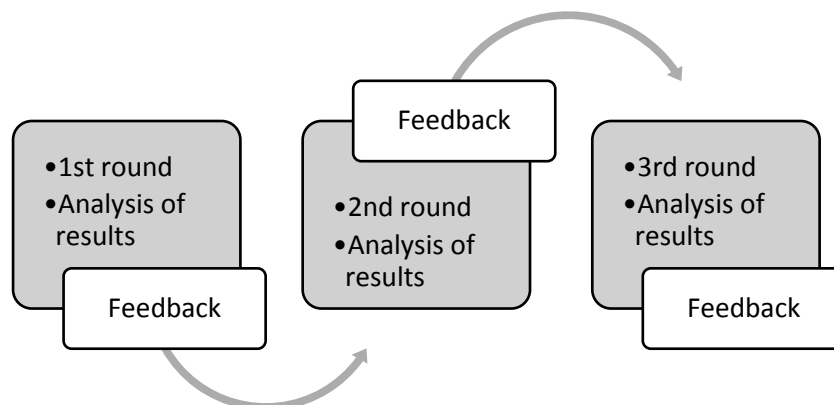
5.2.2 The James Lind Alliance (JLA) Priority Setting Partnerships

The JLA has set up Priority Setting Partnerships (PSPs), focusing on specific conditions or healthcare settings, to raise awareness of research questions that are of direct relevance and potential benefit to patients, carers and clinicians, and to hopefully change the way research funding is granted (JLA Guidebook, n.d.). The JLA method is based on the principles of transparency, inclusivity and avoiding waste in research – investment in research is wasted when wrong choices of research questions are made, research is unnecessary or poorly designed, relevant research is not published promptly or at all, and/or research reports are biased or unusable (Chalmers and Glasziou, 2009; Figure 5b). To

achieve its goals and counteract the imbalance of traditional research agenda setting methods, each PSP prioritises the voices of those who receive or deliver healthcare. Figure 5c shows the overall structure of a PSP.

Figure 5b: Waste occurring at four successive stages of research (Chalmers and Glasziou, 2009)

Questions relevant to clinicians and patients?	Appropriate design and methods?	Accessible full publication?	Unbiased and usable report?
Low priority questions addressed Important outcomes not assessed Clinicians and patients not involved in setting research agendas	Over 50% of studies designed without reference to systematic reviews of existing evidence Over 50% of studies fail to take adequate steps to reduce biases—eg, unconcealed treatment allocation	Over 50% of studies never published in full Biased under-reporting of studies with disappointing results	Over 30% of trial interventions not sufficiently described Over 50% of planned study outcomes not reported Most new research not interpreted in the context of systematic assessment of other relevant evidence

Research waste

The outcome of the PSP prioritisation process is a list of 'top ten' prevention and/or treatment uncertainties for consideration by research funders. The JLA definition of an uncertainty is that:
- no up-to-date, reliable systematic reviews of research evidence addressing the uncertainty about the effects of prevention or treatment exist; or
- up-to-date systematic reviews of research evidence show that uncertainty exists (JLA Guidebook: Chapter 2, n.d.).

Figure 5c: Overall structure of a Priority Setting Partnership (JLA Guidebook: Chapter 3, n.d.)

Wider stakeholders (patients, carers, clinicians)

Partners

Steering Group

JLA Advisor, PSP Leader, PSP Project Coordinator

- PSP members who participate in the prioritisation process
- Represent and can advocate for patients, carers or clinicians
- Organisations or interest groups

- A small group
- Coordinates and implements PSP activity
- Includes patient and clinician representatives, and a JLA Advisor

Each PSP goes through five key stages to obtain a 'top ten' list, as summarised in Figure 5d.

Figure 5d: Summary of the JLA research priority setting process (JLA Guidebook, n.d.; Crowe, n.d.)

1. Initiation
- Define the issue and agree its scope
- Identify potential partners and raise awareness
- Contract for partnership effectiveness, i.e. agree roles, gain ownership, set timelines, etc.
- Establish a Steering Group

2. Consultation
- Gather potential prevention and/or treatment uncertainties:
  - Directly from stakeholders, using standard methods e.g. surveys, interviews, focus groups
  - From existing guidelines and systematic reviews

3. Collation
- Categorise eligible (in-scope) uncertainties, combine similarities, refine and rephrase
- Check existing evidence base to verify the uncertainties (see above definition)
- Submit uncertainties into the UK Database of Uncertainties about the Effects of Treatments (DUET)

4. Prioritisation
- *Interim phase:* Consult with partners to agree a shortlist of uncertainties, via email, post or online. E.g. approaches: Likert scale or choose and rank 10, followed by a reverse scoring system
- *Final phase:* Priority setting workshop done face-to-face with all partner representatives using the Nominal Group Technique to agree 'top 10' uncertainties

5. Reporting and refining
- Refine priorities into good quality research questions
- Report formally to partners and their communities of interest
- Report to funding organisations and allied groups
- Publish in relevant journals, and patient/carer publications

The processes of the Nominal Group Technique (NGT) are illustrated in Figure 5e – this and the Delphi technique mentioned above, are both known as consensus methods. The main difference between the two methods is that the NGT requires face-to-face meetings, which can be difficult to organise, but it can generate results more promptly than the Delphi technique, which can take weeks or months to conclude if multiple rounds are required (McMillan *et al.*, 2016).

Figure 5e: Processes of the Nominal Group Technique
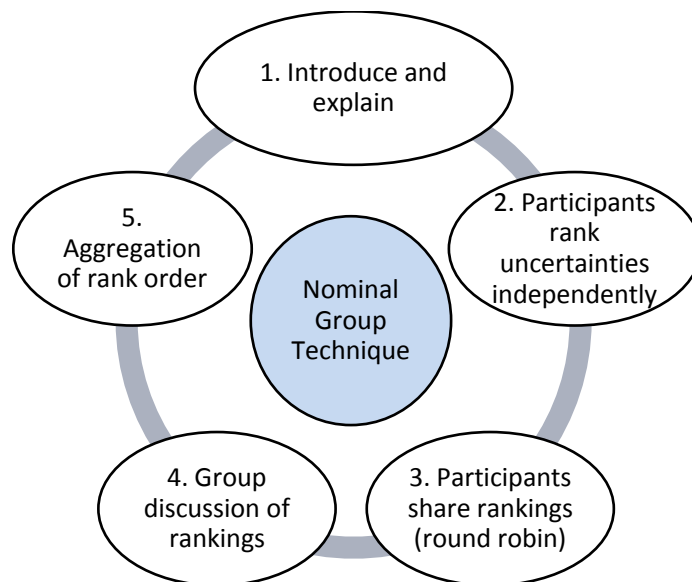
5.3   Critical analysis of the Dialogue Model and JLA approach

The most notable differences between the Dialogue Model and the JLA approach are when and how the prioritisation process occurs:

The Dialogue Model
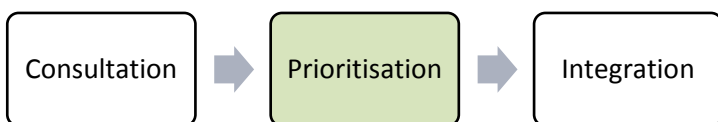
Identification and prioritisation of research agendas occur separately for each stakeholder group; dialogue between stakeholders only takes place in the integration phase. This approach anticipates that the differences between stakeholders prevent meaningful interaction early in the process, i.e. professionals may dominate the interaction with patients. Therefore, before successful dialogue can occur, patients need to be empowered and prepared for a more equal interaction with professionals, while professionals need to be sensitised to respect patients for their knowledge gained through experience (Abma and Broerse, 2010).

The JLA approach
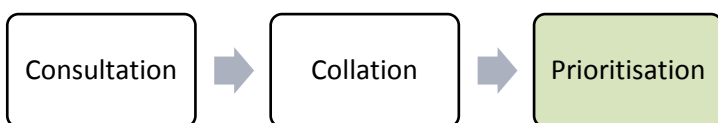
The Steering Group and project partners collaborate in the prioritisation stage, which occurs later in the agenda setting process compared to the Dialogue Model. PSPs are advised that they must ensure patients are

as confident and empowered as clinicians to submit their treatment uncertainties during the consultation stage (JLA Guidebook: Chapter 6, n.d.).

Members of PPIPAD agreed that patients would need to gain confidence to participate in the priority setting process, regardless of which approach is used. The process would need to be guided by clearly established criteria against which stakeholders would assess the importance of the research topics/treatment uncertainties to be prioritised in terms of their impact on, for example, patients' quality of life and functionality.

Several PPIPAD members voiced their preference for one approach over the other:

> "Patients are going to have more input if they're with other patients, rather than against the professionals." [Val, PPIPAD, on the Dialogue Model]

> "I quite like the (Dialogue Model) because if you have all the patients and the carers in a room together and they're discussing, at least then, even when you integrate them together with the professionals and it gets kind of blurred, at least you've got definitive priorities of what the patients and carers are interested in and the professionals as well, so you could kind of mould them together." [Tom, PPIPAD]

> "It would be quite interesting then, to look at the priorities and see how different or how similar they were." [Andy, Associate Professor in PPI, in response to Tom's comment]

> "I think it's important to prioritise later in the process so that you get a wide range of views. If you prioritise early on as you do in the Dialogue Model, you're likely to eliminate some of the thoughts and suggestions. If you let them all come out and then prioritise them, you're likely to get a wider range of opinion. I would favour the Priority Setting Partnership." [Richard C., PPIPAD]

Although the JLA approach has the advantage of being a clear and transparent process that provides equal opportunity for input, the final priority setting workshop is time-limited. Thus, the panel raised a question about whether the outcome would be a true consensus, since the PSP would be left with whatever the outcome was when the time ended.

5.4 Alternative approach

The Dialogue Model and the JLA approach both require the recruitment of a fairly substantial number of participants before consultation can take place. Although this is desirable for representativeness and may work well for issues related to long-term conditions, the panel felt that it may be impractical for more acute conditions such as infections. This is evidenced by the Healthcare Associated Infections (HCAI) PSP, where they had experienced difficulties in collecting enough responses, particularly from patients (Case Example 5b). Actual details on why patients were deterred from getting involved in the HCAI PSP were not available, but the panel had some thoughts on what the perceived barriers might have been:

> "…as soon as you're better you can think, well, I'm off, (I've got) the rest of my life out there." [Roy, PPIPAD]

"I think it's also how it is put forward to people... The amount of surveys that you get bombarded with today is ridiculous. So if all they did was to send out a survey, then you may very well get a negative reaction. Depends on how it is sold to the people that you want to take part." [David R., PPIPAD]

"Infections are a bit non-descript... not as tangible almost, when you say it's an infection. Maybe that's part of what the barrier is, because it's so broad... When you know it's something wrong with your arm or you've got cancer, you know, it's very specific... I think it (also) depends on the patient group that (the James Lind Alliance) are approaching. The average patient group would probably not – they'd struggle to get interest. But if you target patient groups that have an interest in infections and antibiotics, and know the bugs they get, and what antibiotics they have, and what treats what, because they are expert patients, they would have completed their surveys, no problem." [Angelo, PPIPAD]

The panel discussed and agreed that the lack of 'sufficient' responses should not be a deterrent for the priority setting process to proceed; that it is more important to have some patient involvement in the research agenda setting process, rather than worrying about the process being completely rigorous.

"It's nice if you can get a lot of people, but don't be too discouraged if you don't and proceed anyway with what you've got... don't stop and go home if you don't get too many, press on with the few or how many you managed to muster." [Richard C., PPIPAD]

As a result of discussions with the panel, an alternative approach was proposed: instead of gathering a large number of issues from a wide group of stakeholders and narrowing them down, ideas should be generated by a relatively small group of patients. Professionals should be involved in an advisory capacity as early on as possible, i.e. they should be invited to workshops where patients' ideas are shared and offer advice when necessary. They would then collaborate in the development of those ideas that are realistic, feasible, and most important to patients. Although the number of research questions produced in this manner may be relatively small, they should hopefully be quite well put together, therefore increasing their chances of being taken forward by potential research funders – evidence of academic and clinician support is crucial to achieve this. This approach is a simple and potentially quicker alternative that should keep everyone engaged. As one panel member put it:

"I think you need to start off simple, as much as you can, and then you expand it, and you take everybody along. If you start off with a too complex model or ideas, I don't think you're going to get the group to go along with it." [Roy, PPIPAD]

To ensure that patients' voices are prioritised during the agenda setting process, it is recommended that there be a clear definition of the role of academics as advisors only, and not active participants in the discussion – a strong project lead or chief facilitator would be required to ensure this.

The necessity of involving the pharmaceutical industry in this process was discussed with the panel. There was concern that they would be *"representing their own company and not the general public"*, and that they would *"find a way of engineering control of the group and their ideas"*. However, it was acknowledged that pharmaceutical industry involvement would potentially *"add a lot of weight"* and increase the likelihood of a research agenda being picked up. It was decided that there is potential to involve pharmaceutical companies in a similar advisory capacity as academics, subject to good moderation of roles by the facilitator.

Case Example 5b: The James Lind Alliance Healthcare-Associated Infections Priority Setting Partnership

Healthcare-associated infections (HCAIs) are the most frequent adverse event in healthcare delivery worldwide. Consequences of HCAIs include an estimated annual cost of at least £1bn to the NHS, at least 5,000 deaths per year, and a major impact on patients and their families due to prolonged hospital stays.

The HCAI Priority Setting Partnership (PSP) was established in early 2015 with the aim of identifying and prioritising uncertainties around prevention, identification and treatment options for HCAIs. The Steering Group that led and managed this PSP included patient and clinical representatives. The priority setting process was iterative and dependent on the active participation and contribution of project partners, consisting of:

- people who have had HCAI
- carers of people who have had HCAI
- medical doctors, nurses and professionals allied to medicine with HCAI

At the PSP setup stage, potential partners were identified via a process of peer knowledge and consultation, through the Steering Group members' networks and the James Lind Alliance's (JLA) existing register of affiliates. They were invited to attend and participate in an initial stakeholder meeting, whose agenda included:

(a) Presentation and discussion of the proposed plan for the PSP
(b) Identification and recruitment of committed partners
(c) Establishment of principles upon which an open, inclusive and transparent mechanism can be based for contributing to, reporting and recording the work and progress of the PSP

Subsequently, the Steering Group and project partners worked with patient representatives to design a simple questionnaire to gather uncertainties of practical clinical importance relating to the treatment and management of HCAIs. They tried to get responses via the web, Healthcare Infection Society, healthcare conferences, and other patient charities. They received 60 responses, which was thought to be insufficient.

When contacted, a clinical member of the Steering Group thought that patients were particularly deterred from participating – no further explanation was given. He has since used some personal investigator funds to pay for a research nurse to talk to patients in local hospitals in London, with ethics approval. This change of consultation strategy has successfully gathered a large number of additional responses from both patients and hospital staff. (Personal communication with Professor Peter Wilson, 19th January 2017.)

With over 250 questions collected from the initial survey, the PSP committee has narrowed this down to 50 questions. A second survey is currently underway to gather responses that will help to identify the importance of these questions. This survey closes on 30th June 2018, after which a final priority setting workshop will be conducted.

To find out more about the HCAI PSP, visit http://www.jla.nihr.ac.uk/priority-setting-partnerships/healthcare-associated-infections/.

> **KEY POINTS**
>
> - PPI in research agenda setting demonstrates responsiveness to patients' needs, ensures a democratic process, and improves acceptance of decisions and outcomes; the increased relevance may subsequently lead to improved recruitment and retention in clinical trials.
>
> - The Dialogue Model is a validated approach to facilitating interaction between patients and professionals to establish shared understanding and agendas.
>
> - The JLA PSP approach identifies the top ten prevention and/or top ten treatment uncertainties through a transparent and inclusive process.
>
> - The panel identified pros and cons to each approach, but agreed that patient confidence and empowerment are essential for effective and meaningful participation in the agenda setting process, regardless of method used.
>
> - A simple and potentially time-saving alternative approach was proposed following discussions with the panel. The stakeholders involved and their roles are as follows:
>
>   o Patients – mainly responsible for generating ideas for research questions.
>
>   o Professionals (clinicians and academics) – advisors, and partners in developing ideas that are realistic, feasible and most important to patients.
>
>   o Pharmaceutical industry – advisors *(optional involvement)*; could increase likelihood of a research agenda being taken up.

5.5   References

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6 PPI in drug discovery and preclinical development

ABSTRACT

The earlier stages of drug discovery and preclinical development are often deemed too technical for PPI to have any relevance to success. Through organised workshops, patients within the rare neurological disease community have identified three phases of the drug discovery process that have the potential for meaningful PPI: (i) development of the target product profile, (ii) the lead optimisation stage, and (iii) in the preparation for clinical trials. This chapter will explore those workshop findings that may be applicable to antimicrobial medicines development. We conclude that effective PPI in drug discovery and preclinical development is challenging, and requires pharmaceutical companies to be flexible and adaptable.

6.1 Introduction

Combatting the problem of antimicrobial resistance requires sustained collaborative drug discovery efforts. The path to bringing a novel antimicrobial to clinical trials and subsequently to market, is illustrated in Figure 6a – the funnel analogy characterises the discontinuation of most antimicrobial development programmes as a result of serious problems suffered during later stages of development, for example failed toxicology studies, or inability to scale up the molecule for manufacturing (Hughes and Karlen, 2014).

Figure 6a: The drug discovery process (www.slidegeeks.com/funnel)

NDA: New Drug Application

The likelihood of clinical success for such programmes is, therefore, dependent on the discovery and validation of multiple independent 'hits', and on the quality of these chemical starting points (Hughes and Karlen, 2014; Katsuno *et al.*, 2015). A 'hit' is a chemical compound which has the desired activity, usually derived from screening and whose activity is validated upon retesting (Hughes et al., 2011; Cambridge MedChem Consulting, 2015).

Although the role and value of PPI in the medicines development lifecycle has been gaining recognition among researchers, regulators and pharmaceutical companies, its inclusion occurs primarily at the point of recruitment for first clinical trials; the earlier stages of drug discovery and preclinical development are often deemed too technical for PPI to have any relevance to success (Spencer *et al.*, 2016). Figure 6b shows the percentage of pharmaceutical companies that include PPI at various stages of the medicines development lifecycle, as estimated by the Clinical Trials Transformation Initiative (CTTI), a public-private partnership that includes international government and industry representatives.

Figure 6b: Estimated percentage of pharmaceutical companies globally that include PPI at different stages of medicines development (Ellis, 2016)
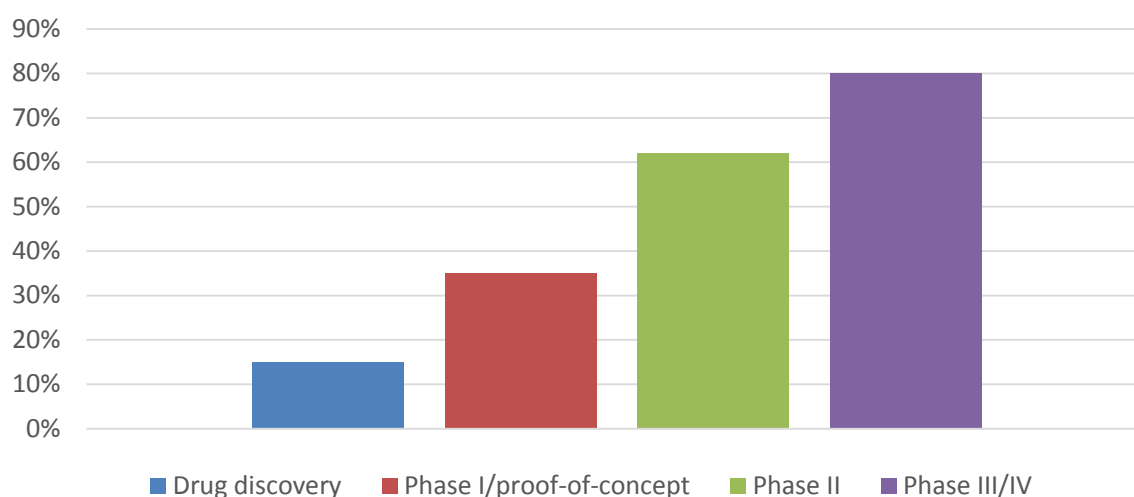
In a recent interview, Julie Adrian, European Managing Director of inVentiv Health Communications, disclosed that there is "a tectonic shift in thinking within big and small pharma towards getting the patient voice into development, even as early as product discovery" (Ellis, 2016). She highlighted several key benefits of PPI during drug discovery and preclinical development:

- The ability to build long-standing relationships, which are particularly important in disease areas where patient numbers are small.
- The opportunity to plan along the continuum from medicines development into commercialisation, which helps to connect clinical insights with commercial models.
- A chance to break down internal silos that divide clinical and commercial activities.
- The ability to develop an early understanding of patient needs within a disease area.
- The opportunity to communicate these insights to regulators. (ibid)

Patients within the rare neurological disease community have participated in workshops, where they identified three phases of the drug discovery process that have the potential for meaningful PPI (Spencer *et al.*, 2016) – some of the workshop findings may be applicable to antimicrobial medicines

development, and will be the focus of this chapter. The philanthropic alliance responsible for this project of integrating rare disease patients into preclinical therapy development, supports early PPI to help target the most meaningful health outcome improvements and avoid mistakes with clinical trial design as treatments enter human studies (ibid).

6.2 Developing the target product profile (TPP)

The TPP is a strategic guidance used by pharmaceutical companies "to facilitate discussions and solicit feedback from regulators on the overall drug development programme for an investigational product" (FDA, 2015, in Lowe *et al.*, 2016). It defines the key features of the drug to be developed. PPI is important at this initiation step in order to develop a TPP that reflects patients' perspectives on disease burden and severity, treatment experience, and unmet needs. The role of PPI here includes participating in the identification and prioritisation of key attributes of the drug, as well as the ideal and acceptable values for these attributes, such as the route of administration, dosing, efficacy, acceptable levels of adverse events, and possibly even willingness to pay (Lowe *et al.*, 2016).

Once developed, companies should continue to involve patients when updating the TPP throughout the development programme, while taking care to maintain acceptable standards (ibid). The TPP, together with preliminary data defining a hit, are used to make an initial evaluation of the economic potential of the drug in the event of successful market entry. The most economically valuable antimicrobials will be those that can be "synthetized easily, modified readily, taken orally, have a wide bioavailability, low toxicity, and can be prescribed for a broad spectrum of bacterial pathogens" – although, in view of the serious problem of antimicrobial resistance, there will also be high interest in molecules for intravenous use, or for a narrow spectrum of pathogens (Hughes and Karlen, 2014).

6.3 Lead optimisation stage

The primary objective of this final drug discovery stage is to maintain or improve on desired activities in lead compounds, while reducing known liabilities (Hughes and Karlen, 2014) – examples of liabilities are induction of the cytochrome P450 enzymes responsible for a large number of drug metabolism reactions, or hampered elimination of the compound from the body. At this stage, PPI has a role in re-assessing the benefit-risk profile and the relevance of proposed clinical endpoints to patients, leading to an update on the TPP with regards to efficacy assessment targets, and objectives of tolerability (acceptable levels of adverse events) and convenience (acceptable drug route and dosing frequency) (Spencer *et al.*, 2016).

Given the high attrition rate in antimicrobial drug development, it is essential for discovery work not to stop at this stage. Ongoing exploration is necessary not only to produce back-up molecules in case the lead compound fails further preclinical or clinical characterisation, but more strategically, to identify a follow-up series and generate a sustainable pipeline of novel hits moving into later-stage development and feeding into clinical trials (Hughes *et al.*, 2011; Hughes and Karlen, 2014).

6.4 Preparation for clinical trials

The benefits of PPI in the early stages of drug discovery and preclinical development are expected to continue into the design of Phase I/II clinical trials, including definition of the eligibility criteria (Spencer *et al.*, 2016). Examples of other potential patient inputs at this stage include:

- Sharing their thoughts on the TPP and the preclinical results with regulators
- Attending regulatory meetings alongside the sponsor
- Collaborating in the design of clinical trials (ibid)

Patients and public contributors would have a new understanding about the challenges of designing and implementing a manufacturing process that can be scaled up from the research lab to human dosing studies, leading to an appreciation of the complexities of clinical trials and possibly a subsequent willingness to be patient and supportive when problems arise (ibid). This would empower them to educate their communities on the medicines development process and facilitate ongoing efforts to promote autonomy and active involvement of patients and the public in health research.

6.5 Potential challenges and facilitating strategies

Ellis (2016) reported on the top five major factors preventing pharmaceutical companies from including PPI in early medicines development, as identified by CTTI: insufficient tools, concern on how to involve patients, internal resistance, lack of funding, and absence of expert patients. Her report also states that companies require a certain degree of flexibility in order for PPI to be effective in the early medicines development process (ibid). While smaller and mid-sized companies have been able to adapt quickly, and therefore encourage the growth of PPI in medicines development, big firms have had to take a different approach to address the lack of flexibility – they are creating more and more micro-organisations within their companies, and introducing chief patient officers and patient engagement leaders to propel these micro-organisations and patient engagement teams (ibid).

> *"If the community said, 'You know what, that's not going to serve our needs the best right now,' the organisation involved would adapt. The company had the cultural flexibility and the corporate courage to say, 'Okay, fine. We're not going to do what we originally planned.'"* [Julie Adrian, inVentiv Health Communications; cited in Ellis, 2016]

A notable point of consensus that emerged from the workshops with patients from the rare neurological disease community was the intention of patient organisations to "collaborate on a template for contracts covering ownership and access to intellectual property (IP), animal models and cell lines, so that access and IP security are assured" (Spencer *et al.*, 2016). The report further describes the patient organisations' support for drug developers to "own the IP in joint projects in a model where the financial (rewards) can be shared with all participants as projects mature" (ibid). The workshops and their output are being used in a co-created blueprint, and the concepts and consensus on practical methods for PPI in drug discovery and preclinical development will be implemented in specific programmes during 2017 (ibid). Any concerns about confidentiality or commercial sensitivity can be alleviated by including appropriate confidentiality clauses in consulting agreements between pharmaceutical companies and public contributors.

A drug development project becomes public knowledge once a candidate enters clinical trials and this clinical phase represents the vast bulk of the expense of medicines development – failure of the project during this phase is not only expensive, but will impact on public confidence in the company

and shareholder value (Hughes *et al.*, 2011; Hughes and Karlen, 2014). Therefore, it is preferable to discard potentially problematic molecules in the early discovery stages (Hughes and Karlen, 2014). Although PPI in the early drug discovery and development stages is still at its infancy and there is a need for more supportive evidence, we suggest that providing continuous information and education to patients and the public, coupled with sufficient sponsor investment into PPI can facilitate a more (cost)-effective process.

> *"Educating patients is important. We ran a session with our health advisory board – which includes patient advocacy groups – where we took them through discovery and development, and explained what we mean by lead optimisation and what a phase I clinical trial involves. Before we did that I would have said there wasn't much value in involving patients in phase I, but the advisory panel said that was exactly when they wanted to be involved because the earlier they are involved the better influence they have."* [Murray Stewart, GlaxoSmithKline; cited in Underwood, 2016]

KEY POINTS

➢ The role of PPI in developing a *target product profile (TPP)*: participate in the identification and prioritisation of key attributes of the drug, as well as the ideal and acceptable values for these attributes.

➢ The role of PPI at the *lead optimisation stage*: re-assess the benefit-risk profile and the relevance of proposed clinical endpoints to patients, to update the TPP.

➢ The role of PPI in the *preparation for clinical trials*: input into clinical trial design; provide feedback to regulators about the TPP and preclinical results.

➢ Effective PPI in drug discovery and preclinical development requires pharmaceutical companies to be flexible and adaptable.

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7 PPI in clinical trials

ABSTRACT

PPI in clinical trials is important for several reasons, including to efficiently generate new and relevant knowledge that benefits future patients, to improve recruitment and retention, and for quicker application of research findings. There is potential to incorporate PPI at all stages across the clinical trial continuum.

This chapter describes the role of PPI at three stages: (i) trial design and protocol development, (ii) trial conduct, and (iii) trial data analysis and dissemination of results. Each stage is discussed in a separate section, and includes practical examples of how PPI has been successfully implemented in clinical trials in various fields of research. We also include quotes from representatives of pharmaceutical companies to provide some insight into their experiences of PPI. We conclude with a discussion of the potential challenges of implementing PPI in clinical trials, and propose strategies to overcoming them.

7.1 Introduction

The Study of Patient-Centric Initiatives in Drug Development conducted jointly by the Drug Information Association (DIA) and the Tufts Center for the Study of Drug Development (Tufts CSDD) found that the benefits of implementing patient-centric drug development initiatives include "reduced screen failure rates, faster patient recruitment rates, improved subject retention rates, reduced numbers of protocol amendments, and a greater number of patient-relevant endpoints" (DIA, 2016). Sacristan *et al*. (2016) and Bagley *et al*. (2016) make similar claims about the importance of having effective and meaningful PPI in clinical trials for the following reasons:

- More efficient generation of new and relevant knowledge to benefit future patients
- Ensure appropriate and ethical research conduct
- Increase recruitment to time and target, and improve participant retention
- Improve accessibility of study results to participants and the wider public
- Quicker application of research findings

There are various stages across the clinical trial continuum that can incorporate PPI (Figure 7a). The first of these occurs pre-trial, where PPI has a role in identifying research priorities – this is described in detail in Chapter 5. PPI in the medicines regulatory process is covered in Chapter 8. Here, we will focus on how to incorporate PPI in clinical trial design and protocol development, trial conduct, and analysis and dissemination of trial results.

Figure 7a: The clinical trial continuum (adapted from Clinical Trials Transformation Initiative, n.d.)
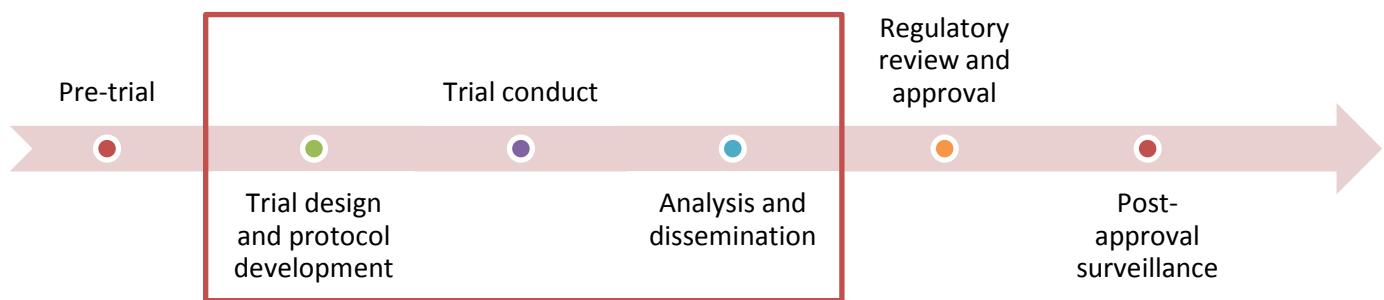
7.2   PPI in trial design and protocol development

It has become increasingly common to involve patients as partners in the design of clinical trials and as members of ethics committees. One of their key roles is in identifying patient-reported outcomes (PROs) or endpoints that are meaningful to them and that "adequately reflect the spectrum of the disease experience and the diversity of the target patient population" (Smith *et al.*, 2016). The use of PROs is expected to rise as a result of regulatory agencies' guidelines on their inclusion in the evaluation of new pharmaceuticals – patients' perspectives would be important in the benefit-risk trade-off analysis throughout a medicine's lifecycle (Sacristan *et al.*, 2016). This necessitates the establishment of a framework for systematic PPI early and continuously throughout the medicines development lifecycle (Smith *et al.*, 2016; Hoos *et al.*, 2015).

"If you ask people in the industry what Parkinson's is about they'll say shaking and that's how all drugs were developed; how well do they control shaking? But we've talked so much with patients now that we've realised the hardest part of living with this disease is not the tremor, which is relatively easy to manage, it's other things like sleep disturbances and gastro problems that have a much greater effect on your life. That will drive your clinical studies and the drugs you go for." [Lode Dewulf, UCB; cited in Underwood, 2016]

"The practicalities of daily life seem more important to patients, which is something regulators hardly ever take into account." [Regulator; cited in Greene, 2015]

Case Example 7a: PPI in identifying outcomes that are meaningful and relevant to patients (Dures *et al.*, 2017)

Patients with psoriatic arthritis identified important treatment outcomes beyond those that are commonly measured. A key example is *fatigue* – its impact and the ineffectiveness of some treatments to improve it. Unlike pain, an outcome regularly identified by patients but one that is widely measured, fatigue is not routinely addressed in either research or clinical practice. The study pointed out that outcomes identified reflect patients' treatment beliefs and influence their treatment decisions, such as the likelihood of taking their medicines properly (adherence). It highlighted the need to establish how identified outcomes are represented in existing measures.

Besides defining outcome measures, patients can assist in defining the eligibility criteria and advise on the recruitment strategy, such as highlighting any potential barriers to participation (NIHR RDS,

2014). All patients who meet the eligibility criteria and wish to participate, should have access to do so. Recommendations to improve patients' access to clinical research include:

- Ensuring trials are set up to prevent inequalities in factors such as socioeconomic status, ethnicity, and type of health insurance.
- Enhancing and standardising information about ongoing trials and about the participating sites, for example, in clinical trial databases and patient associations.
- Embedding clinical research into clinical practice, that is "point-of-care research", for example, evaluating health interventions used in normal clinical practice in comparative effectiveness studies. (Sacristan *et al.*, 2016)

Patient insight is useful in designing clinical trials that patients actually want to take part in, thus helping to drive recruitment and retention.

"By bringing patients in we found that they don't like the typical phase I, placebo-control study, because they are pretty sick and they don't want to miss out on a drug that might work. We told them that there is another study design, a delayed onset study, where you start half the patients on placebo and then move them on to the drug at a later stage. The patients liked that idea. They also said 'why does placebo have to be so long, at this stage does that really matter, don't you just want to know if the drug works for us?' They then pointed out that they can tell us in half of the time of the regulators. We agreed, so we've been simplifying studies and making them more interesting for patients and it's been wonderful." [Lode Dewulf, UCB; cited in Underwood, 2016]

"Bringing patients into the scientific realm creates a sense of reality and adds a dose of pragmatism." [Murray Stewart, GlaxoSmithKline; cited in Underwood, 2016]

Case Example 7b: PPI in defining the eligibility criteria and advising on recruitment strategy (CTTI, 2015)

The *Foundation for Prader-Willi Research (FPWR)* attended a sponsor meeting to review a protocol for a regulatory trial. FPWR noted the protocol had exclusion criteria, which listed medications that caregivers reported were commonly used by their children in the age range targeted for the study. FPWR then worked with the sponsor to change the protocol and modify the exclusion criteria, which otherwise would have been a significant barrier to participant recruitment to time and target.

Written information (i.e. the informed consent form and patient information sheet) provided to clinical trial participants or their legal representatives to obtain informed consent must be "comprehensive, concise, clear, relevant, and understandable to a layperson" (European Parliament, 2014, Article 29.2(b)). This is essential so that participants understand the following aspects:

- The purpose of clinical research is to generate useful information for future patients and therapeutic benefit cannot be guaranteed.
- There is a possibility, due to random allocation, that they may be assigned to a placebo.
- There is a risk of exposure to adverse effects.

The role of PPI here includes:
  - designing and ensuring readability of the informed consent documents
  - reviewing and evaluating simplified versions of the document to be used in low-risk point-of-care trials

- creating decision aids to help ensure that the consent granted by patients is truly informed (Sacristan *et al.*, 2016; CTTI, n.d.).

PPI can also ensure that the chosen methods are appropriate to patients' needs and lifestyles, and are ethically acceptable – this includes reviewing and commenting on the proposed research tools, such as questionnaires and patient diaries (Bagley *et al.*, 2016; NIHR RDS, 2014). Other ways in which PPI can contribute in developing the research protocol include informing areas where the patient and public perspective would be important, raising awareness about the costs of PPI, and advising on the appropriateness of the lay summary (ibid).

Case Examples 7c: PPI in designing and reviewing patient-related materials

Example 1 (Gale *et al.*, 2016; Hassan, n.d.)

Gale *et al.* investigated the acceptability of novel methodological approaches used as part of simple, large, efficient clinical trials to UK Research Ethics Committees (RECs). They developed a protocol for the WHEAT (WithHolding Enteral feeds Around packed red cell Transfusion) neonatal comparative effectiveness trial with extensive parent and parent group involvement:

- the research question is based on a James Lind Alliance Priority Setting Partnership
- parent focus groups informed trial design
- parents have been on the trial development group from its outset
- parents wrote the initial draft of the participant information sheet (PIS)

With the support of the UK Health Research Authority (HRA), an identical application was submitted to 12 RECs, proposing a point-of-care trial with an "opt-out" model of consent and a streamlined PIS. The results highlighted variable decision-making: whilst nine RECs granted a favourable opinion, three rejected the application because they considered the "opt-out" consent process invalid. One REC was concerned about the short PIS, though this was resolved after parental involvement in the design was demonstrated. The median time from REC meeting to final decision was 14 working days (range 4-33). The authors concluded that, whilst there were some discrepancies, the majority of RECs in this study considered the methodological approaches acceptable in neonatal comparative effectiveness trials.

Example 2 (European Patients' Academy on Therapeutic Innovation, 2017)

Input from a patient consumer group resulted in revisions of the parental patient information leaflet (PIL), and child and adolescent assent forms: the use of much more patient-friendly wording, and avoiding business, technical and medical terminology (e.g. sponsor, vendor, and subject). Not only was there appreciation from the patient point of view, the review timeline from the Ethical Review Board (ERB) was also shortened to just 20 days from ERB meeting to approval being issued, with very few comments received on the documents.

Example 3 (Ennis and Wykes, 2016; 2013)

Analysis of 522 information sheets from the UK National Institute for Health Research (NIHR) Clinical Research Network: Mental Health portfolio database and study principal investigators found that a higher level of patient involvement facilitated briefer information sheets, which was associated with higher likelihood of successful recruitment to target. In an earlier study, the same authors reported a possible dose-response relationship – studies which included researcher-initiated collaboration were 1.63 times more likely to recruit to target than studies that only consulted patients (i.e. lowest level of involvement), whereas studies that included the highest level of involvement (i.e. jointly-initiated collaboration, patient-initiated collaboration, and patient-controlled studies) were 4.12 times more likely to recruit to target.

7.3   PPI in clinical trial conduct

There are three distinct levels of clinical trial conduct where PPI may be incorporated – an individual trial, a group or programme of related trials, or a clinical trials unit or research department – each with its own set of potential benefits and challenges, as set out in Table 7a. PPI may contribute to a range of activities that include:

- supporting trial operations and clinical infrastructure
- advising on any trial adaptations or modifications (see Case Examples 7d)
- acting as peer advocates during the recruitment of trial participants
- ensure that researchers remain accountable throughout the trial
- help to clarify misperceptions or to resolve any misunderstandings between trial participants and pharmaceutical sponsors (CTTI, 2015)

It should be noted that not all of the above may be feasible in trials related to antimicrobial drug development.

Case Examples 7d: PPI in influencing trial adaptations and modifications to improve trial conduct and recruitment

Example 1 (Dyakova *et al.*, 2017; personal communication with Dr Jonathan Otter, 9th March 2017)

A large prevalence study for ESBL-Enterobacteriaceae (ESBL-E) required rectal swabs for optimum detection of colonisation. PPI was included in developing and reviewing patient information materials used in the study, but not in training staff for the consent and recruitment process. The percentage of patients declining to provide a rectal swab (i.e. participate in the study) after week 1 was 50% – these patients associated with many of the risk factors for antibiotic-resistant bacteria, particularly age and gender. High variability was observed in the way that staff approached patients and verbalised the study description. Patients' feedback during the review process influenced the development of improved staff training materials. The revised study description was much simpler and focused on patient benefit. As a result, the decline rate significantly reduced from 31.9% (n=869) to 7.6% (n=3690; p<0.001).

Example 2 (Donovan *et al.*, 2002)

Qualitative findings showed that recruiters in the ProtecT (prostate testing for cancer and treatment) study had difficulty discussing equipoise (i.e. a state of genuine uncertainty regarding the comparative therapeutic benefits of each arm in a trial) and presenting treatments equally; they also unknowingly used terminology that was misinterpreted by patients. Changes were made to the trial conduct:

- Changes to the order of presenting treatments encouraged emphasis on equivalence
- Misinterpreted terms were avoided
- The non-radical arm was redefined as "active monitoring" instead of "watchful waiting" or "wait-and-see", to avoid conveying an impression of wilful neglect
- Randomisation and clinical equipoise were presented more convincingly

One of the key learning points is that changes to the content and delivery of study information increased recruitment rates from 40% to 70%.

Table 7a: Potential benefits and challenges of PPI at different levels of clinical trial conduct (INVOLVE, 2012)

PPI at different levels of clinical trial conduct	Potential benefits	Potential challenges
1. Involvement in an individual trial	• Establishes strong working relationships between individuals on the Trial Management Group (TMG) • Gives different perspectives to members of the trial team, e.g. on specific problems that may emerge within a trial • Influences trial adaptations and modifications to improve trial conduct and recruitment • Ensures that the members of the public involved, fully understand the specific trial and its value • Assists with dissemination of results, e.g. via charities or patient groups, or by providing a patient story or perspective • Furthers the professional development or training of trial team members • Helps with future or other ongoing trials, e.g. in establishing standard wording or structure for patient information	• Asking for long-term commitment to a new trial expected to take many years to complete may be hard, e.g. for people living with a life-threatening condition • Identifying individuals who are best in a position to contribute • Ensuring that people's opinions are heard and valued by the trial team • Providing individualised training and support for members of the public, which could be time and resource intensive • Retaining interest during periods when there may seem to be little or nothing happening with the trial • Maintaining involvement and avoiding disappointment when trials do not get funded
2. Involvement in a group or programme of related trials	• Works with people who have first-hand experience and knowledge • Establishes and builds relationships that potentially lead to regular collaboration throughout the trial process • Provides an opportunity for people to develop more strategic roles within the trial programme as they become more experienced, e.g. influencing the design of new trials, becoming co-applicants on trial grants, and so on • Gives members of the public a chance to build their skills over time	• Finding appropriate people – especially in under-researched areas • Providing training and ongoing support for those involved, which may have time and resource implications • Sustaining involvement over a prolonged period, especially if there are periods when no trials are happening
3. Involvement in a clinical trials unit or research department	• Places involvement at a strategic level • Ensures consistent involvement in all trials conducted within a unit • Builds familiarity between researchers, who may feel more confident approaching members of the public who they know and vice versa • Facilitates quick responses to specific issues, by drawing on existing expertise and skills of involved people • Coordinates involvement across many trials, by helping individuals to feel less isolated and providing support and mentorship	• Excludes input or experiences from people who may not be keen to be involved at a strategic level in a large organisation or department • Overlooks important issues that may be specific to the disease or topic area • Relies on the input of a small group of individuals that may not be benefiting from the opinions of others • Increases the burden of responsibility on individuals who are involved

7.4 PPI in trial data analysis and dissemination of results

It is important to consult patients and members of the public to check for coherence in the understanding and interpretation of trial data. Once finalised, aggregate results should be returned to trial participants ahead of dissemination to the scientific community – this step is not only ethical, but respects their willingness to volunteer and their partnership in research (MRCT Center, 2016; Sacristan *et al.*, 2016). PPI can assist in the preparation of these plain language summaries of trial results to be returned to participants.

Evaluating the opinions and experiences of clinical trial participants is useful to improve the design of future studies and increase their acceptance by clinicians and patients. PPI can contribute to this by assisting in the analysis of participant feedback regarding things like trial sites and investigators, and motivations for participation. For example, results of several surveys to assess participants' experience indicate that over 90% of patients who participated in clinical trials were motivated by their willingness to help future patients (Sacristan *et al.*, 2016). This is an important finding that challenges the 'therapeutic misconception' and advocates for greater patient autonomy in research. A 'therapeutic misconception' exists when "individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial" (Henderson et al., 2007).

There are various avenues for disseminating trial results and PPI can play an active role in the preparation of documents containing these information, to ensure that the language and messages used are more easily understood by the general public, and that the format of communication is simple and accessible:

- The European Clinical Trials Database (EudraCT): Sponsors of clinical trials are obligated to make publicly available the details of each study, including a summary of the results. ClinicalTrials.gov is another resource that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies, including synopses of trial results.

- Scientific journals: Some journals have taken the initiative to publish "summaries for patients", and brief and approachable reviews of common diseases and their treatments. The *British Medical Journal* has taken its commitment to patient partnership a step further by including patients in the peer review process for research articles.

- Clinical practice guidelines (CPGs): PPI in research would only be meaningful if their experiences are used to improve care. Hence, there needs to be joint working between patients and experts in the preparation of CPGs to ensure that patient perspectives and preferences are considered.

- Other opportunities for dissemination: Newsletter articles, blogs, websites of charities or voluntary organisations, informal patient networks, and joint presentation with researchers. (Sacristan *et al.*, 2016; NIHR RDS, 2014; CTTI, n.d.)

An open and transparent approach to sharing of clinical trial data could potentially generate greater confidence in the research findings, and improve clinical trial participation and funding –

recommendations and standards have been established by the Institute of Medicine (Lo, 2015) and European Medicines Agency (Bonini *et al.*, 2014) to guide this process.

Among the growing number of examples of PPI in clinical trials, Boote *et al.* (2016) have provided a detailed account of how parents and children with asthma were involved in the design and conduct of the PLEASANT trial through two PPI consultation events: pre-grant submission and post-award, pre-commencement, with a further consultation planned for the end of the trial to gather input for the disseminating strategy. They describe various techniques for actively involving children in the trial design process, and also report on the usefulness of the post-award, pre-commencement consultation to provide feedback to the PPI contributors on how their input contributed to successful grant capture (ibid).

7.5   Potential challenges and facilitating strategies

PPI in clinical trials, and medicines development in general, is not without its challenges, whether real or perceived. Stakeholders need to be aware of the added time, complexity and cost of PPI, while also anticipate its potential value to the overall trial process (Boote *et al.*, 2011; Lowe *et al.*, 2016). Senior (2016) acknowledges that "more targeted, efficiently recruited, technology-enabled trials that are less disruptive to patients' lives and engage them more fully in the process are not only patient-centric but also make economic sense for pharma – they are likely to retain more patients, generate richer data, progress faster and thus be cheaper".

Communication between stakeholders, including the pharmaceutical industry, and patients may be impacted by legal, compliance and regulatory restrictions – while the need to report patient-informed adverse events is a real challenge, concerns about legal or regulatory statutes prohibiting direct interactions with patients represent more imagined barriers (Hoos *et* al., 2015; Lowe *et al.*, 2016). Concerns about whether direct contact with patients about a trial development programme would be seen as promoting an unapproved product may be alleviated by engaging patients on a disease-focused basis and/or using consulting agreements (Senior, 2016).

> *"We thought we weren't allowed to do it. Everyone told us that there was no point in going to the FDA because they are going to say 'no'. In fact we went, and they said 'yes'."*
> *[Melissa Jean Mottolo, a Roche Patient Recruitment Strategist; cited in Hodgson, 2015]*

The research team may perceive patients as having a self-serving agenda or limited contribution, despite being given opportunity and support, or there may be a lack of mutual trust and respect, openness and reciprocity (Bagley *et al.*, 2016; Hoos *et al.*, 2015; Senior, 2016). Patients themselves may find it challenging to understand trial methodology sufficiently to make meaningful contributions (Boote *et al.*, 2011). Overall, advocates of PPI in medicines development activities face an uphill battle to enact change among healthcare decision-makers (Lowe *et al.*, 2016).

A study examining PPI in clinical trials and UK Clinical Research Collaboration (UKCRC) registered Clinical Trials Units (CTUs) found that PPI works well if there are clear goals and well-developed plans for PPI in a trial, and if models of PPI favour responsive and managerial roles rather than oversight roles in steering committees – these roles are described in Table 7b (Gamble *et al*., 2015).

Table 7b: Three main types of roles for PPI contributors (Gamble *et al.*, 2015)

Oversight role	Formal involvement in the trial on multiple but infrequent occasions, e.g. as a member of the Trial Steering Committee (TSC), meeting six-monthly or annually
Managerial role	Formal involvement on a more regular basis, e.g. as a co-investigator or as a member of the Trial Management Group (TMG)
Responsive role	Impromptu and more informal involvement – approached as difficulties arose, e.g. if people took too long to fill in questionnaires; also includes advising on patient information sheets, troubleshooting recruitment difficulties and tailoring interventions, methods of data collection and follow-up to the needs of patients

Patients must be treated as collaborators and equal partners in every aspect of the clinical trial process in order to improve its quality and efficiency (Hoos *et al.*, 2015; Lowe *et al.*, 2016). The implementation of PPI in clinical trials requires ongoing information and education to promote autonomy and the active involvement of patients. To accomplish this, healthcare professionals, regulatory agencies, patient associations, and pharmaceutical companies need to collaborate to:

- Inform the general public about the aims and processes of research, as well as the mechanisms available to protect study participants – this would improve the health literacy of potential patient partners and facilitate shared decision-making. This can be done through a variety of ways, including the internet, digital media resources, and the industry's medical information departments.
- Educate and empower patients to be experts in research through training courses designed to provide specific knowledge on the clinical trial process, such as that offered by the European Patients' Academy on Therapeutic Innovation (EUPATI) (Sacristan *et al.*, 2016).

Lowe *et al.* (2016) have proposed a range of solutions for increasing the level of PPI in the medicines development process, including the barriers identified above. The Patient Focused Medicine Development (PFMD) coalition of industry firms and the patient community aims to collaborate with other stakeholders (e.g. regulators, payers) to establish a framework for more harmonised patient engagement across the sector, share best practices, and address cultural, communication, legal and regulatory barriers (Senior, 2016). A Patient-Inspired Knowledge Hub to assemble best practice and guidelines around PPI in drug development is being developed with the support of the Innovative Medicines Initiative (IMI; ibid). Bagley *et al.* (2016) are developing a toolkit to facilitate meaningful and effective PPI at all stages of a clinical trial. To date, they have described the PPI pathway through a trial and have presented preliminary findings on existing 'off-the-shelf' online resources and additional resources required to promote clear planning of PPI from the outset, encourage a considered approach to involvement activities, and support researchers in the rapid development of clinical trials, not just in the UK but also in other countries (Bagley *et al*., 2016).

> **KEY POINTS**
>
> - There is potential to incorporate PPI at all stages across the clinical trial continuum, and there are benefits and challenges associated with it.
>
> - The role of PPI in *trial design* and *protocol development*: advise on relevancy of PROs and outcome measures; improve access to and recruitment of participants; assist in the development of patient-related materials (informed consent documents, data collection tools); ensure a continuous approach to PPI throughout the trial, and not a fragmented, "one-off" approach.
>
> - The role of PPI in *clinical trial conduct*: support trial operations and clinical infrastructure; advise on any trial adaptations or modifications; ensure accountability of researchers.
>
> - The role of PPI in *trial data analysis* and *dissemination of results*: ensure coherence in the understanding and interpretation of trial data; contribute to the analysis of participant feedback on trial experiences; assist in the development of patient-level communication.
>
> - The successful implementation of PPI in clinical trials requires clear goals and well-developed plans for responsive and managerial PPI roles, equal partnership, and the provision of ongoing information and education to empower and facilitate the active involvement of patients.

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8 PPI in regulatory review and approval

ABSTRACT

PPI in regulatory review and approval is important to support the transparency, communication and sharing of data that underpin regulatory decisions. The European Medicines Agency (EMA) and United States Food and Drug Administration (US FDA) have established a range of independent schemes to facilitate PPI in the regulatory process.

This chapter describes the various ways in which patients can contribute to the regulatory review and approval process. We include examples of how PPI has had an influence in advisory committee meetings and public hearings by both the EMA and FDA. We also briefly describe the collaborative workgroup known as the Patient Engagement Cluster set up by these two agencies. We conclude by discussing the potential challenges and facilitating strategies associated with PPI in regulatory processes.

8.1   Introduction

In recognition of the unique position of patients to provide essential insights about what it is like to live with and fight an infection or other medical condition, there have been increasing demands for greater patient involvement in the work of regulatory authorities to support the transparency, communication and sharing of data that underpin regulatory decisions. Expanding the patient's role in regulatory benefit-risk assessments via ''the more thoughtful identification and compassionate use of the individual patients' predicaments, rights, and preferences in making clinical decisions about their care,'' can help to reduce the uncertainty about the degree and type of risks that are tolerable in the context of a particular medicine's benefits in the intended patient population (Smith *et al.*, 2016).

Patient thought leaders interviewed by Lowe *et al*. (2016) felt that regulators "do not always have a complete understanding of the risks that patients with some illnesses are willing to accept, and that this benefit-risk assessment will vary by disease"; they also expressed that "they may be willing to accept more risks to get the right treatment sooner" – similar patient sentiments have been reported by Gingery (2016b). Regulators have also acknowledged the value of PPI in the decision-making process:

> *"In essence, I think the decision-making is enriched and better by having patient reps involved."* [Regulator A; cited in Greene, 2015]

> *"By involving patient representatives, it has turned out that they had very different views of what is important. My experience is also that patient representatives have been willing to take greater risks than the regulators would like them to do."* [Regulator B; cited in Greene, 2015]

To answer this call for action, both the European Union (EU) and the United States (US), have established a range of schemes to facilitate PPI in the regulatory process. A revised EU pharmacovigilance legislation in 2012 led to the implementation of a new system for managing the safety of marketed medicines, which "resulted in faster detection of safety issues and allowed regulators to take rapid action to provide warnings and advice to users of medicines" (Schofield, 2016). The European Medicines Agency (EMA) revised their framework for interacting with patients and consumers to better incorporate those stakeholders' values and preferences in regulatory decision-making (Bonini *et al.*, 2014). The EMA has also developed and published guidance for PPI in benefit-risk discussion and evaluation within its scientific committees, working parties, and scientific advisory groups, to ensure that involvement is consistent and efficient (EMA, 2014).

The fifth reauthorisation of the Prescription Drug User Fee Act (PDUFA V) under the US Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 has led to the development of programmes and initiatives that provide various opportunities for PPI in the medicines development and review process, including the Patient-Focused Drug Development (PFDD) initiative – which allows patients to speak directly with FDA about their risk tolerance and unmet needs – and Professional Affairs and Stakeholder Engagement Staff (PASES) (FDA, 2015). FDA has also developed a structured Benefit-Risk Assessment Framework that provides a more systematic and comprehensive approach to obtaining the patient perspective on a medicine's benefits and risks. FDA is committed to implementing this framework and has a 5-year plan for its further development and implementation to improve the regulatory decision-making process (ibid). It is anticipated that the 21st Century Cures Act, signed into law in December 2016, will enhance these ongoing efforts to better incorporate the patient's voice into FDA's decision-making (Califf, 2016).

8.2   PPI in the regulatory process

There are various ways in which patients and the public can contribute to the regulatory review and approval process. The following are examples of the role of PPI, pre- and post-approval:

Examples of pre-approval PPI:
- Difficult applications, especially where there is a real or perceived need for the medicine
- Unclear medicine efficacy (small or in doubt, or of questionable clinical relevance or patient benefit)
- Unclear medicine safety (occurrence or frequency of serious adverse effects)
- Proposed refusal of marketing authorisation or on appeal

Examples of post-approval PPI:
- New safety issues having a significant effect on the benefit-risk of a medicine
- Shortage or lack of supply of important or essential medicines

The European Patients' Academy (EUPATI) has developed guidance for PPI in regulatory processes, with suggested working practices adapted from EMA that includes patient input to a range of activities along the regulatory process (Figure 8a).

Figure 8a: Overview of patient involvement along the medicines lifecycle at EMA (2016)
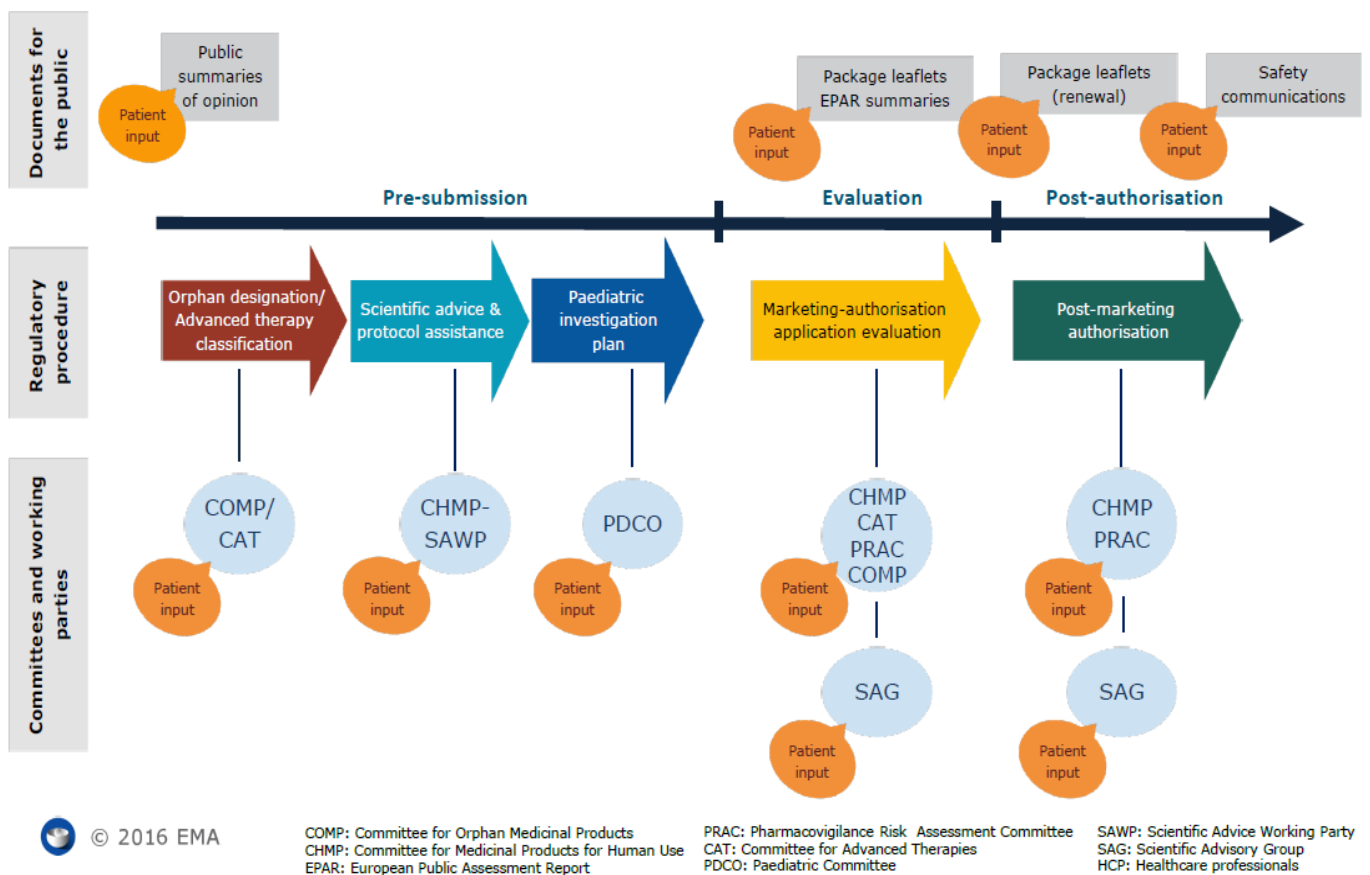
The EMA describes three categories of patient involvement in regulatory activities (Bere, 2016):

8.2.1 Activities in which patients represent patients in general

- EMA Management Board
- EMA Scientific Committees

Patients who are members of scientific committees have equal rights, and contribute to discussions and initiatives in the same way as all other members. The added value of their inclusion depends on their effectiveness in delivering their unique and critical perspective throughout the committee's activities and outcome, based on their real-life experience of being affected by a medical condition and its current therapeutic environment (either personally or as a carer), thus promoting safer and more rational use of medicines.

8.2.2 Activities in which patients represent their organisations

- EMA Patients' and Consumers' Working Party (PCWP)
  - Key role in the interaction between the EMA and patient organisations
  - Platform for dialogue and exchange on relevant issues concerning medicines
  - Representation from patient and consumer organisations, EMA scientific committees and the Management Board
  - Four meetings held annually and consulted as and when needed
- EMA conferences and workshops
- Preparation of guidelines – patients are sent draft guidelines for comments

8.2.3 Activities involving individual patient experts

- **Medicines development:** Participation in scientific advice/protocol assistance procedures for specific medicines
- **Evaluation of medicines benefit-risk**: Pre- and post-authorisation; participation in expert meetings convened by committees; written consultations on specific medicines from scientific committees/working parties
- **Communication on medicines**: Review of information on medicines – Package leaflets, European Public Assessment Report (EPAR) summaries, safety communications, and other EMA documents for the public

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has been given the mandate to conduct public hearings on the safety of marketed medicines (Article 20 of Regulation (EC) No 726/2004 and Articles 31 or 107i of Directive 2001/83/EC), thus creating a new tool for increased PPI in the regulation of medicines (Sharma, 2016). A director at Eurordis, an organisation that represents patients with rare diseases, has welcomed this development, saying that it can instil public confidence in the regulatory procedures in addition to supporting the regulatory decision-making process (ibid).

Case Example 8a: PPI in PRAC's first public hearing (EMA, 2017; EMA, 2018)

On 26 September 2017, EMA's PRAC held a public hearing in an ongoing safety review looking at measures to reduce the risks of the antiepileptic drug, valproate, in pregnancy and women of childbearing age. The 65 attendees comprised patients and patient representatives, healthcare professionals, academics, pharmaceutical industry, and the media. Personal testimony of patients, families, and individuals exposed to valproate before birth helped the PRAC gain insight.

There was general agreement of the undeniable and well characterised risks of valproate to the unborn baby if used during pregnancy. However, in considering the effectiveness of current measures, the public confirmed that information resources were not reaching the right people at the right time. Dissemination, implementation and acceptance of the need for change had not happened as intended, thus the hoped-for strengthening of risk minimisation had not been evident. Participants at the public hearing provided important ideas, thoughts and suggestions on how to further reduce the risks, which the PRAC reflected on and debated to form its conclusions.

Following this latest safety review, the PRAC concluded that women often still do not receive appropriate information about valproate in a timely manner and that further measures are needed to reduce exposure during pregnancy. In February 2018, the PRAC recommended new measures to avoid valproate use in pregnant women, including new restrictions on use, a pregnancy prevention programme, and valproate product package changes. These new measures were endorsed by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) on 23 March 2018. The CMDh position was agreed by majority vote, so it has been sent to the European Commission, which will take a final legally binding decision valid across the EU.

In the US, patients serve on FDA advisory committees as consumer representatives and provide testimony at FDA hearings, during the review and approval process (CTTI, 2015). It has held over 20 PFDD meetings with patients and representatives from various disease areas to better understand disease severity and the adequacy of current treatments (Senior, 2016).

Case Examples 8b: PPI in FDA advisory committee meetings/open public hearings

Example 1 (Gingery, 2016a)

A combination of sponsor choice and FDA support have allowed a Duchenne muscular dystrophy advocacy group to present patient-reported outcomes (PROs) during the sponsor's formal presentation on the proposed treatment, eteplirsen (*Exondys 51*) – this is believed to be a first for an advisory committee meeting. The advocacy group's presentation included data from patient and caregiver interviews, which yielded unexpected findings not seen in the normal progression of the disease: they found that boys taking eteplirsen had no or less spontaneous falls, and also had their weakness and fatigue decreased or stabilised over time. Patient experience data was intended to provide additional context to the clinical endpoints, which FDA had questioned after concluding that the historical data that the sponsor had relied on as a control did not differ much from the results of patients who were on treatment. Eteplirsen was eventually approved by FDA.

Example 2 (Silverman, 2016)

The oncolytic virus therapy, *Imlygic*, was granted full approval following patient and caregiver testimony at a FDA advisory committee meeting about the cosmetic and psychological advantages of seeing melanoma lesions shrink – this testimony was a key factor in convincing FDA to accept the novel primary endpoint of 'lesion shrinkage' as clinically meaningful, despite the absence of positive overall survival data. This primary endpoint, formally known as durable response rate (DRR), had never before been used to support FDA approval.

> *"There may not be metrics that adequately capture the value of watching a tumour disappear, but I was persuaded by the patients, their caregivers, and the physicians who served on the advisory committee that DRR is clinically meaningful."* [Wilson Bryan, Director, Center for Biologics Evaluation and Research Division of Clinical Evaluation and Pharmacology/Toxicology]

8.3   The EMA/FDA Patient Engagement Cluster

International collaboration and information exchange related to medicines development and approval is essential to public health – the EMA and US FDA collaborate in workgroups called 'clusters'. In June 2016, a Patient Engagement Cluster was established with the primary goal of sharing best practices on involving patients along the medicines' regulatory lifecycle within the respective agencies, to further improve and extend each agency's current activities in this area. This cluster will discuss:

- Ways for finding patients that appropriately speak for their community
- Ways to ensure that patients involved in agency processes directly voice the concerns of their community
- Ways to train selected patients and advocates to effectively participate in agency activities
- Strategies for reporting the significant impact of patient involvement (FDA, 2016)

The terms of reference for this cluster are available at
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/06/WC500209197.pdf.

8.4   Potential challenges and facilitating strategies

PPI can strengthen the regulatory benefit-risk decision-making process, but it may also raise additional issues with the benefit-risk decision itself due to the fundamental tension between the ''good'' (preferences, values) of the individual versus that of society as a whole. Specifically, while infected individuals might find the benefits of an antimicrobial to outweigh its rare risk, for example, of causing birth defects (i.e. teratogenicity), from a public health perspective, even a single case of developmental abnormality might be considered unacceptable. This is an area where PPI in partnership with regulators and pharmaceutical companies need to not only assess the probability, expected frequency and severity of an adverse event occurring, but also to include effective risk-mitigation strategies (Smith *et al.*, 2016). For example, in the case of teratogenic risk, the partnership should consider recommending the use of contraception if the antimicrobial is deemed to have an appropriate level of benefit to justify this risk.

Inclusion of patient testimony at public hearings constitutes meaningful evidence, but can make it challenging for regulators to weigh it against clinical data (Gingery, 2016a). Nevertheless, FDA seems determined to play its role in evolving patient-focused drug development and is currently considering the idea of establishing a central office to coordinate patient engagement activities across programmes, and to provide a "more transparent, accessible and robust experience for patient communities" (Gingery, 2017). In terms of regulatory policy, the Biotechnology Innovation Organization (BIO) and the Pharmaceutical Research and Manufacturers of America (PhRMA) have criticised the process of gathering patient input through disease-focused meetings under PDUFA V as being "anecdotal" in nature, and have requested for a more structured and data-driven process to be put in place under PDUFA VI (Sutter, 2014), a proposal that FDA is prepared to take on board (Gingery, 2016b).

KEY POINTS

➤ PPI in regulatory review and approval is important to support the transparency, communication and sharing of data that underpin regulatory decisions.

➤ The EMA and FDA have established a range of independent schemes to facilitate PPI in the regulatory process. Both agencies have also set up a collaborative workgroup to share best practices in regulatory PPI**.**

➤ Patients can be involved in various pre- and post-approval processes along the medicines lifecycle. Their involvement can be as representatives of patients in general, representatives of patient organisations, or as individual experts.

➤ Patient testimonies at EMA and FDA hearings can provide meaningful evidence to support regulatory decision-making.

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9   Approaches to PPI

ABSTRACT

Among the wide array of approaches to PPI in research, the two that are most relevant to antimicrobial medicines development are *consultation* and *collaboration*. This chapter describes these approaches, and their associated benefits and challenges. We provide examples from real-world research of how the public can be involved in grant applications, and through workshops, patient and public forums, reference groups, advisory panels and steering groups. The choice of which PPI approach to employ will depend on the nature of the research and the types of activities available for people to contribute to.

9.1   Introduction

There are various methods of involving public contributors in research depending on the nature of the research, and the different activities at different stages that are available for people to contribute to. The method of involvement chosen will in turn influence the number of public contributors you involve. There are two broad approaches to PPI that are relevant to antimicrobial medicines development research: consultation and collaboration (Table 9a).

Table 9a: Approaches to PPI in antimicrobial medicines development research (INVOLVE, 2012)

	Consultation	Collaboration
	Public contributors are asked for their views and advice on any aspect of the research process	Shared decision-making between researchers and public contributors
Benefits	- Useful when exploring sensitive and difficult issues - Elicits a wide range of views - Involves people in discussion and debate	- Helps to ensure research remains focused, relevant and ethical - Skills and perspectives of researchers can complement those of public contributors - Improves recruitment and informed consent
Challenges	- Might not elicit the broad views hoped for - People might have previous negative experiences of consultation where their views were not listened to - Requires an experienced facilitator	- Resource-demanding: Human resources (e.g. preparation and administrative work), time, additional cost - Requires training and support for all involved - Requires researchers to be flexible and willing to share control of the research

Consultations can be single or repeated events, and can involve individuals or groups of public members; the groups may be convened especially for the consultation or may be established patient organisations (Nilsen *et al.*, 2006). INVOLVE (2012) offers the following advice to facilitate consultations with public contributors:

- Give them enough time to respond
- Feedback on the actions taken as a result of the consultation
- Ask if they would like to be informed about the findings of the research

Collaboration involves professionals working together with public contributors to achieve a collective outcome. It is based on the underlying principle that those affected by the outcome of research are best placed to help design, participate in, and implement it (Imperial College Health Partners, 2016; adapted from ParticipationCompass.org).

[Participation Compass](#) is a decision tool that researchers can use to assist them in identifying appropriate methods for involving public contributors, based on responses to the following questions:

- What is the main change you are trying to achieve?
- How much money do you have available for the process?
- Do you need to involve a certain number of people?
- What type of people do you want to involve?
- Do you have a preference for face-to-face or online processes?

The following sections describe examples of how to involve public contributors in research through consultation and collaboration. The boundaries between these two approaches are not clear cut, and they usually co-exist within a research project.

9.2   Grant applications

The public is increasingly involved in providing their perspective on research grant applications and funding processes. They can contribute to:

- improving the design and focus of the research
- advise on 'best practice' for PPI throughout the research
- advise on ethical issues (INVOLVE, 2006)

Responsibilities of public contributors may include reading, reviewing and preparing a written critique for all assigned applications, participating in review panel meetings, and providing feedback to the research or funding organisation in follow-up surveys (PCORI, n.d.).

There are various ways of identifying people to get involved in co-writing or reviewing grant applications, which may include contacting and creating links with one or more of the following:

- Voluntary organisations relevant to the research topic(s) under consideration
- Organisations that represent or are led by patients
- Individuals with a specific experience or from a particular group (INVOLVE, 2006)

Tip Box 4 describes a process for seeking public input into research grant applications – this example is applicable when there is a local organisation providing support and advice to researchers who want PPI. However, if no such organisation exists, the following approaches may be helpful to find people to get involved:

- Ask colleagues with experience of PPI, if any.
- Directly approach other relevant organisations, such as community groups, carer support groups, GP surgeries/family physicians and pharmacies. (INVOLVE, 2006)
- Use suggestions in Tip Box 2 (page 15) to seek out potential public contributors.

TIP BOX 4: HOW TO… seek public input into research grant applications. (Involving People in Research, 2017)

1. Contact the local organisation that provides support and advice for researchers who want to have PPI in their research projects.

2. Meet with the PPI representative or advocate to discuss the project and how you would want to involve people with lived experience to provide input into the research.

3. Co-produce an advertisement in plain language and distribute.

4. Wait for a response from a potential public member.

5. The organisation's PPI officer can help facilitate an initial meeting with the interested public member.

6. Send a draft application to the public member with specific information on what aspects require feedback.

7. Meet with the public member, take notes, and arrange payment.

8. Receive feedback from the PPI officer on the process and interactions with the public member.

9. Amend the grant application based on public member feedback.

10. If appropriate, invite the public member to be a co-investigator on the project.

9.3   Workshops

Workshops are guided discussions of a small group of public contributors. Although workshops tend to be one-off sessions, multiple sessions may be run simultaneously in different locations (Imperial College Health Partners, 2016; adapted from ParticipationCompass.org).

Benefits	Challenges
• Small group size facilitates high level of interaction • Ideal for getting opinions from people who would not be prepared to give written answers • Allow researchers to gain a better understanding of how people think about or approach an issue	• Highly dependent on a skilled facilitator • Easily dominated by one or two strong voices, which may inhibit others from speaking • May not be able to use qualitative responses to gauge wider opinion

9.4   Patient and public forums

Forums can be used to gather views or input from large groups of people in a short period of time. Issues that may be discussed in forums include:

- the design of a specific research project
- priorities for new research
- the potential impact of research to patients and the public
- research outcomes or findings (Involving People in Research, 2017)

Case Examples 9a

Example 1: Telethon Kids Institute Youth Forum (Involving People in Research, 2017)

This forum was set up by the Telethon Kids Institute in Australia to consult young people aged 15-25 years about their thoughts on health and wellbeing, and how to make the youth voice heard in the work of the Institute. The forum was promoted through youth networks and on social media. Forty young people attended on the night, where payment and pizza were offered. They shared their views on the following:

- What are some of the things about health and wellbeing that you and your friends talk about?
- How can we (the Institute) find a variety of young people to have a say about research?
- How do you want to have a say?

Example 2: The European Patients' Forum (EPF, 2017)

The European Patients' Forum (EPF) comprises representatives from specific chronic disease groups at EU level or from national coalitions of patients. It is an umbrella organisation that supports the work and mission of patient groups in public health and health advocacy across Europe, through capacity building initiatives and exchange of best practices and information. From January 2017, EPF has been leading a campaign on Access to Healthcare.

9.5   Reference groups

Reference groups comprising members of the public can be established for consultation at a particular stage or throughout the course of a research project. The role of reference groups may include:

- having representative(s) on the main research team who report back to the reference group
- getting information out about research activities being planned
- helping to develop an appropriate strategy for disseminating research findings (Involving People in Research, 2017)

Case Example 9b: Infectious Diseases Community Reference Group 2007-2014 (Involving People in Research, 2017)

The reference group was established not only to provide guidance on what research was important to the community, but also to assist in explaining the purpose and results of research to the community. The eight public contributors in the group included representatives from areas where there are higher levels of infectious diseases. The reference group met four times a year to discuss the progress of infection-related research projects, as well as a chosen topic by a guest speaker. Public involvement had an impact on research priorities, and resulted in better communication of science through the development of plain language summaries.

9.6   Public advisory panellists or groups

Public advisors, either as individual panellists or as a group, work together with researchers to provide advice at a strategic level to inform decision-making over an extended period of time. They create effective and ongoing dialogue that enables issues and concerns to be explored and addressed appropriately (Imperial College Health Partners, 2016; adapted from ParticipationCompass.org). Depending on the nature of the research and advice required, public advisors might need good expertise on the health condition or research area (i.e. expert patient), and/or good research and development (R&D) experience.

Benefits	Challenges
- Can spot early signs of potential problems and be a useful sounding board to test plans and ideas - Relationships formed through regular meetings over extended periods of time can facilitate discussions - Advisory groups bring a fresh perspective to discussions and encourage innovation - The more transparent process increases accountability in governance	- Difficult to recruit and retain members due to the long-term commitment required - Drop out can cause membership to become less representative over time; advisory groups may need to be renewed regularly

Case Examples 9c

Example 1: Advisory Panel on Clinical Trials (PCORI, n.d.)

The Advisory Panel on Clinical Trials was established in November 2013 and includes representatives of researchers and patients. It provides advice on multiple aspects pertaining to the selection, research design, implementation, and technical issues of clinical trials for patient-centred outcomes research, including research conducted in typical community settings and relating to important patient subgroups and other parameters of research.

Example 2: Patient Sounding Board (EUPATI, 2017)

A Patient Sounding Board, focused on diabetes and haemophilia, was set up as a collaborative effort between two patient organisations with a pharmaceutical company. The types of patients involved were those with personal disease experience, and expert patients with good expertise on disease and little or good R&D experience. Benefits as a result of this collaboration:

- New perspectives related to PPI were identified
- Detailed inputs from the Sounding Board led to adjustments in specific global projects to optimise particular aspects from a patient's perspective
- Improved understanding that it is possible and of great value to obtain patients' perspectives on a range of issues

Case Examples 9c (continued)

Example 3: PREFER Patient Advisory Group (PREFER, n.d.)

The Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER) project is funded by the Innovative Medicines Initiative (IMI). Its purpose is to "establish recommendations to support development of guidelines for industry, Regulatory Authorities, and Health Technology Assessment (HTA) bodies on how and when to include patient perspectives on benefits and risks of medicinal products". The PREFER Patient Advisory Group (PAG) mainly comprises four patient organisations, coordinated by the European Cancer Patients Coalition (ECPC). It also has a number of individual patients with rheumatoid arthritis involved through the clinical research partners at the University of Birmingham, UK. The PAG members share common expectations and are responsible for ensuring that the methodologies identified correspond to the patient views, experiences and preferences.

9.7 Steering groups

Steering groups comprise other stakeholders as well as public contributors, who share responsibility for ensuring that research protocol is followed, and providing advice and troubleshooting if necessary (INVOLVE, 2017). This is high-level involvement, where public contributors will have more influence on strategic decisions, and should be involved from a very early stage in the project (Involving People in Research, 2017).

Case Example 9d: Seniors Consumer Panel (Involving People in Research, 2017)

The Seniors Consumer Panel (also known as a steering group) was established to facilitate ongoing PPI throughout two research projects. The Panel provided:
- A consumer perspective and input to the research team
- Ongoing advice and guidance regarding issues on chronic illness and medication safety that were important to patients aged 65 years and above
- Representative membership on the research management committee

Some of the tasks undertaken by the Panel included:
- Co-developing workshops to further explore key topics and issues raised at public forums
- Attending workshops to discuss research findings with researchers and health professionals
- Supporting and advocating for changes to policy and practice relating to clear dosing instructions on prescription medicines
- Presenting about PPI activities in the two research projects at a national-level research conference

The impact of the Panel has been significant for both the research projects and in bringing about a definite and measurable change in attitude on the benefits of PPI.

9.8   References

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10 Evaluating the process and impact of PPI

ABSTRACT

There are many reasons why it is important to evaluate PPI in research, including to inform the PPI evidence base, to enhance the quality of PPI as well as the research, and to report back to research funders and public contributors. PPI evaluation methods range from simple to in-depth, depending on the level of robustness required.

This chapter describes two methods in detail: (i) the *'cube' framework* for evaluating the process of PPI in research based on four key dimensions with immediately available results, and (ii) a basic *impact log* for recording and evaluating the outcomes of PPI in research. We also briefly describe the latest revision of the Guidance for Reporting Involvement of Patients and the Public (GRIPP2) checklists, useful for reporting PPI in research papers. Information on more comprehensive approaches to planning and executing PPI evaluation, namely the Public Involvement Impact Assessment Framework (PiiAF) and realist evaluation, are presented in a separate guidance document.

10.1 Introduction

It is important to evaluate PPI in research to:
- improve the quality of PPI, and hence the quality of research
- evidence the impact of PPI and encourage stakeholders to commit to having PPI in research
- justify funding and other resources for PPI, especially in times of financial constraint
- inform members of the public of the difference that they have made
- facilitate planning for future projects, e.g. taking steps to avoid harm or limitations

To achieve these objectives, both the *process* and *impact* of PPI should be evaluated. The approaches to evaluating PPI in research are wide-ranging, from simple to in-depth, depending on the level of robustness required i.e. greater robustness requires more in-depth methods.

Here, we briefly describe quick and simple methods for evaluating the process and impact of PPI in research. More in-depth approaches are described in a separate guidance document, namely:

- The Public Involvement Impact Assessment Framework (PiiAF), which helps you consider how best to involve the public in your research and design a PPI impact assessment plan.
- Realist evaluation, to identify what works for whom (*outcome*) in what circumstances and in what respects (*context*), and how (*mechanism*).

10.2 The 'cube' framework for PPI process evaluation

In Chapter 2, we introduced Gibson *et al.*'s (2017) four-dimensional 'cube' framework as a way of conceptualising *knowledge spaces*, where exchange of different forms of knowledge takes place between researchers and the public they involve (Figure 10a). The 'cube' characterises the dynamic nature of interactions within knowledge spaces – individuals or groups can move within these spaces according to their personal circumstances or nature of the knowledge space.

Figure 10a: The 'cube' framework for evaluating PPI processes/interactions (Gibson *et al.*, 2017)
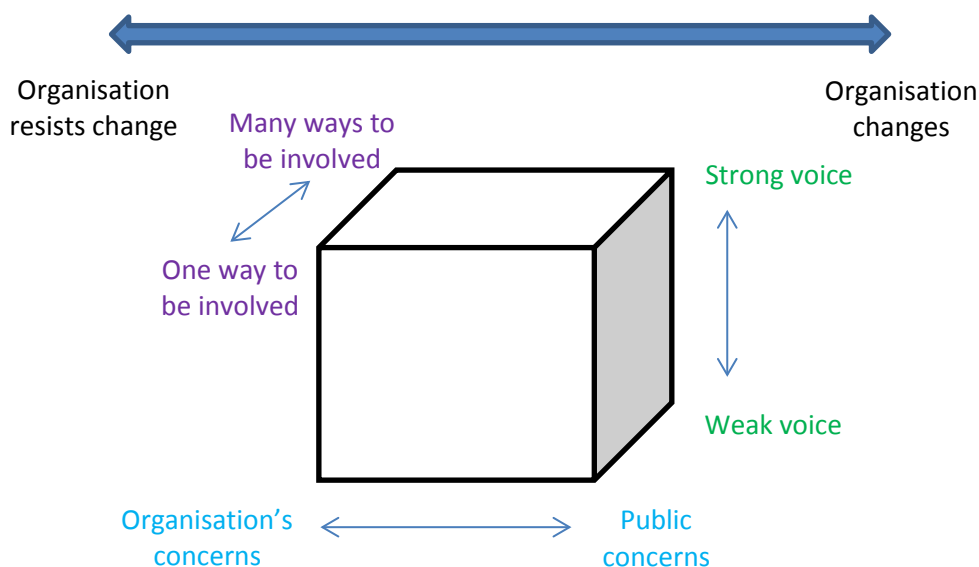
As well as being a useful tool for planning PPI, the framework can be used to evaluate the process of PPI in research. To use the framework for PPI process evaluation, members of a PPI group will be required to participate in a workshop with the format as laid out in Table 10a.

Table 10a: Proposed workshop format to evaluate PPI using the 'cube' framework (Gibson *et al.*, 2017)

Approximate timings	Activities
30 minutes	Introduction to the framework and its origins, including time for questions and answers
1 hour	Exercise to anonymously map experiences of involvement along the four dimensions – these may include experiences of being involved as members of a public panel within a parent organisation and/or involvement in specific research projects as PPI representatives: • Each dimension is separately represented on a wall chart • Ask participants to use a sticky note with an arrow on it to indicate where along the dimension they feel best represents their own PPI experience • Invite them to also write comments on other sticky notes explaining or supporting their arrow placement (illustrated in Figure 10b)
1.5 hours	Discussion and interpretation of the results from the mapping exercise: • Ask participants for comments or reflections, taking each dimension in turn • Have a general discussion about the group's responses and future directions, and obtain feedback on what worked well and what could be improved

Figure 10b: Example wall chart from workshop showing the dimension 'one way to be involved or many ways to be involved'
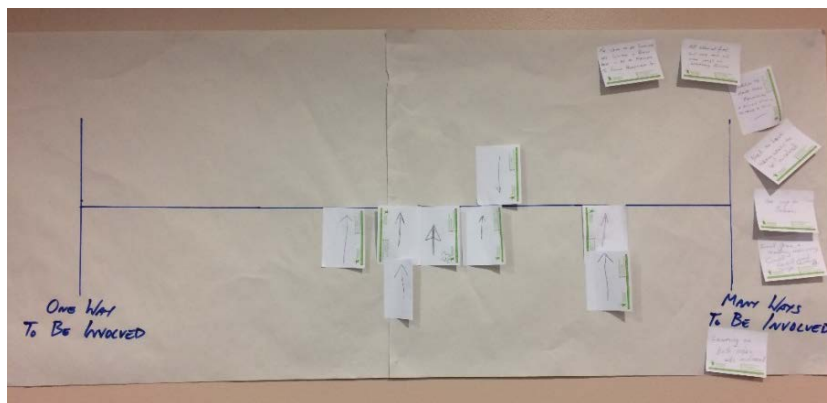
Workshop data is presented in a crosshair design, which provides a simple, accurate and easily interpretable method to plot data from all four dimensions in one diagram (Figure 10c).

Figure 10c: Example mapping of workshop data into a crosshair diagram – the dimension 'one way to be involved or many ways to be involved' corresponds to Figure 10b
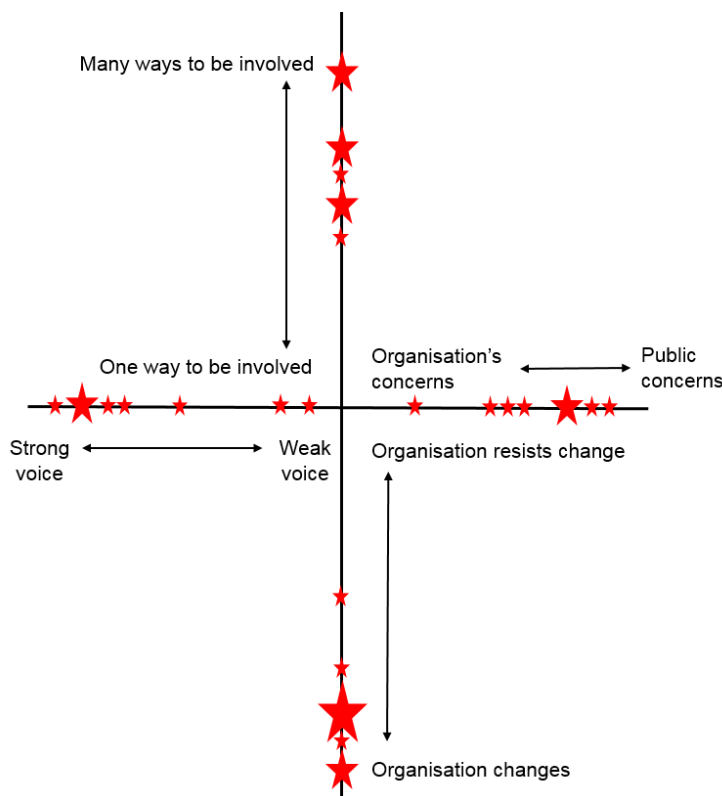
Interpretation of the diagram:

- Responses clustered around the centre of the cross represent a group with a weak voice, limited ways to be involved, little consideration of public concerns and limited opportunities for organisational change.
- Responses towards the extremities of the cross represent a group with a stronger voice, perceived ability to exert organisational change and so on.

- The size of the symbol used is proportional to the number of responses at the same point on a dimension, i.e. a symbol size of 0.5 point is used to represent one person's response, while a 1.5 point symbol would represent three people's responses.

Benefits of using the 'cube' framework:
- Enables cross-sectional comparisons between PPI groups in different organisations, or between different involvement activities within a single group; also allows longitudinal evaluation of changes in PPI interactions over time.
- Results of the mapping exercise are immediately available, allowing areas or activities where there is cause for concern and require appropriate remedial action to be identified in real time. It is useful to note that non-responses may be important indicators of a breakdown in PPI interactions and highlight opportunities to develop more embedded PPI.
- Encourages public contributors to reflect about their involvement experiences and interactions from a more holistic, long-term perspective, and also in relation to the views of other group members and PPI leads.
- The workshop creates a space for collaborative reflection on the purpose and strategic direction of individual and group involvement in the organisation or specific project, and planning of future PPI activities. Its participatory nature helps develop a sense of group cohesion and co-production. (Gibson *et al.*, 2017)

10.3 Impact log to record the outcomes of PPI

Proper documentation of the various PPI activities carried out during the course of research is useful for monitoring and evaluating PPI. Table 10b shows how the outcomes of PPI can be recorded in an impact log (see Appendix 4 for template). In cases where PPI consultations are conducted via email instead of a face-to-face meeting, you may prefer to record the start and end dates as it may take several days for the outcome to become apparent.

This simple log, however, may not necessarily constitute an 'evaluation'. A realist evaluation, such as that used in the RAPPORT (ReseArch with Patient and Public invOlvement: a RealisT evaluation) study, may be more appropriate if you require a more robust evaluation of the impact of PPI. Whichever method you choose, evaluating the impact of PPI in research is important, not only to contribute to the PPI evidence base but also for reporting to research funders, and public contributors.

Table 10b: Example of a research project impact log for PPI

Date	Attendees	Discussion	Impact (Outcomes)	Other comments
dd/mm/yy	Prof. AB Prof. CD Mrs. EF Mr. GH Mr. IJ KL MN Apologies: Mrs. ZY Mr. XW Mr. VU	The existing *[project name]* questionnaire was made available and patient panel members were asked to rate each question based on how important/relevant the issue was to them. Patient panel members were invited to provide their responses anonymously if preferred. The panel was also asked to comment on the domains or themes each question related to. Comments were gathered from the panel.	[From notes of dd/mm/yy] There was some discussion on why certain questions deemed "definitely important" in this patient panel exercise were not included in the final questionnaire, whilst others voted only "quite important" were instead used. CD explained that psychometric and statistical analysis helped to distinguish what questions performed most effectively. This information was used alongside the panel input to decide on which questions to take forward. These results were then used to refine the questionnaire for the next cycle, and help make a decision on which questions to put forward for the final version of the questionnaire.	Copies of the draft questionnaires before and after the panel meetings as evidence of the impact of the panel's contribution.

10.4 Reporting PPI in research papers

PPI in research, both its process and impact, is often underreported or inconsistently reported in research papers. To enhance the quality, transparency, and consistency of the PPI evidence base, Staniszewska *et al.* (2017) developed the GRIPP2 checklists. These are the first international, evidence-based, community consensus informed guidelines for reporting PPI in research (ibid). There are two forms of the GRIPP2 reporting checklists:

(a) GRIPP2-LF (long form; see URL link above)
- Recommended for PPI-focused studies
- Includes 34 items on aims, definitions, concepts and theory, methods, stages and nature of involvement, context, capture or measurement of impact, outcomes, economic assessment, and reflections

(b) GRIPP2-SF (short form; Table 10c)
- Suitable for studies where PPI is not the primary focus, e.g. PPI in clinical trials
- Has five items on aims, methods, results, outcomes, and critical perspective

Table 10c: GRIPP2-SF checklist (Staniszewska *et al.*, 2017)

Section and topic	Item	Reported on page no.
1: Aim	Report the aim of PPI in the study	
2: Methods	Provide a clear description of the methods used for PPI in the study	
3: Study results	Outcomes—Report the results of PPI in the study, including both positive and negative outcomes	
4: Discussion and conclusions	Outcomes—Comment on the extent to which PPI influenced the study overall. Describe positive and negative effects	
5: Reflections/critical perspective	Comment critically on the study, reflecting on the things that went well and those that did not, so others can learn from this experience	

Both checklists can be used prospectively to plan PPI in studies and retrospectively to report PPI in research. Although the authors, Staniszewska *et al*. (2017), recommend careful consideration of the relevance of each checklist item, they also acknowledge that it is not always necessary or possible to include each item in a particular manuscript. Nevertheless, the aim is to guide more effective synthesis of the PPI evidence base, which "will help to identify best practice, avoid poor practice, and contribute to research that is acceptable, relevant, appropriate, and high quality and that has the potential to generate benefit for all" (ibid).

KEY POINTS

➢ The *'cube' framework* provides a quick and simple method for evaluating the process of PPI in research based on four key dimensions:
  o Weak voice or strong voice
  o One way to be involved or many ways to be involved
  o Organisation's concerns or public concerns
  o Organisation changes or organisation resists change

➢ An impact log is a basic way of recording and evaluating the outcomes of PPI in research.

➢ Information on more comprehensive approaches to planning and executing PPI evaluation is presented in a separate guidance document.

➢ The GRIPP2 checklists provide useful guidance for reporting PPI in research papers.

10.5 Reference

Gibson A., Welsman J. and Britten N. (2017). Evaluating patient and public involvement in health research: from theoretical model to practical workshop. *Health Expectations* 1-10. Doi: 10.1111/hex.12486.

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11 Conclusion

ABSTRACT

In this concluding chapter, we have compiled the key points from previous chapters as a quick and easy reference on how to involve the public in antimicrobial medicines development research. Please see individual chapters for more information, including practical examples, where available.

11.1 The basics of PPI

- PPI is not an intervention, but rather a conversation or knowledge space, where researchers and the public exchange ideas, values, assumptions and experiences.
- Researchers should consider involving a group of public contributors that is diverse in terms of experiential knowledge that is most relevant to the context of the project.
- PPI should happen at every stage of the antimicrobial medicines development lifecycle as there is potential for learning to lead to positive impacts throughout the lifecycle.

11.2 Creating links with patients and the public

- The search for public contributors should consider who you want to involve, what you want them for, and what time commitment you require from them.
- At least two and up to twelve members of the public may be involved, depending on the role or activity they will be involved in.
- Various strategies can be used to look for different people with different perspectives needed for antimicrobial research. All those who respond are invited to an initial meeting to receive more information, ask questions, and complete a short expression of interest form.
- Challenges of seeking public contributors: requires a lot of time, commitment and determination; no established patient support groups or voluntary organisations in the area of acute infectious disease; high chance of self-selection; difficult to secure funding to sustain the PPI group.
- Facilitating strategies: personal contact with people who have experience of acute infections, especially those who are concerned with the impact of antimicrobial resistance in wider society, have a sense of wanting to give something back, and feel like they have something to offer.
- PPI in research does not require ethical approval <u>unless</u> the members of the public involved will be collecting and analysing data. Confidentiality clauses can be included in consulting agreements between pharmaceutical companies and public contributors to alleviate any concerns about legal or regulatory restrictions.

11.3 Planning and preparing for PPI

Planning and preparing for PPI requires consideration of the following:

- Strategic planning of organisational responsibilities for effective and efficient implementation of PPI activities

- Costs and payments of expenses to public contributors
- Training and support for researchers and public contributors
- Accessibility – communication format and methods, as well as meeting venue and time
- Meetings – planning, conducting and feedback afterwards
- Documentation of PPI activities for impact evaluation and reporting

11.4 PPI in setting the research agenda

- PPI in research agenda setting demonstrates responsiveness to patients' needs, ensures a democratic process, and improves acceptance of decisions and outcomes; the increased relevance may subsequently lead to improved recruitment and retention in clinical trials.
- The Dialogue Model is a validated approach to facilitating interaction between patients and professionals to establish shared understanding and agendas.
- The JLA PSP approach identifies the top ten prevention and/or top ten treatment uncertainties through a transparent and inclusive process.
- The panel identified pros and cons to each approach, but agreed that patient confidence and empowerment are essential for effective and meaningful participation in the agenda setting process, regardless of method used.
- A simple and potentially time-saving alternative approach was proposed following discussions with the panel. The stakeholders involved and their roles are as follows:
  - Patients – mainly responsible for generating ideas for research questions
  - Professionals (clinicians and academics) – advisors, and partners in developing ideas that are realistic, feasible and most important to patients
  - Pharmaceutical industry – advisors *(optional involvement)*; could increase likelihood of a research agenda being taken up

11.5 PPI in drug discovery and preclinical development

- The role of PPI in developing a *target product profile (TPP)*: participate in the identification and prioritisation of key attributes of the drug, as well as the ideal and acceptable values for these attributes.
- The role of PPI at the *lead optimisation stage*: re-assess the benefit-risk profile and the relevance of proposed clinical endpoints to patients, to update the TPP.
- The role of PPI in the *preparation for clinical trials*: input into clinical trial design; provide feedback to regulators about the TPP and preclinical results.
- Effective PPI in drug discovery and preclinical development requires pharmaceutical companies to be flexible and adaptable.

11.6 PPI in clinical trials

- There is potential to incorporate PPI at all stages across the clinical trial continuum, and there are benefits and challenges associated with it.
- The role of PPI in *trial design* and *protocol development*: advise on relevancy of PROs and outcome measures; improve access to and recruitment of participants; assist in the development of patient-

related materials (informed consent documents, data collection tools); ensure a continuous approach to PPI throughout the trial, and not a fragmented, "one-off" approach.

- The role of PPI in *clinical trial conduct*: support trial operations and clinical infrastructure; advise on any trial adaptations or modifications; ensure accountability of researchers.

- The role of PPI in *trial data analysis* and *dissemination of results*: ensure coherence in the understanding and interpretation of trial data; contribute to the analysis of participant feedback on trial experiences; assist in the development of patient-level communication.

- The successful implementation of PPI in clinical trials requires clear goals and well-developed plans for responsive and managerial PPI roles, equal partnership, and the provision of ongoing information and education to empower and facilitate the active involvement of patients.

11.7 PPI in regulatory review and approval

- PPI in regulatory review and approval is important to support the transparency, communication and sharing of data that underpin regulatory decisions.

- The EMA and FDA have established a range of independent schemes to facilitate PPI in the regulatory process. Both agencies have also set up a collaborative workgroup to share best practices in regulatory PPI**.**

- Patients can be involved in various pre- and post-approval processes along the medicines lifecycle. Their involvement can be as representatives of patients in general, representatives of patient organisations, or as individual experts.

- Patient testimonies at EMA and FDA hearings can provide meaningful evidence to support regulatory decision-making.

11.8 Approaches to PPI

There are two broad approaches to PPI in antimicrobial medicines development research, each with its own set of benefits and challenges:

- Consultation – public contributors are asked for their views and advice on any aspect of the research process

- Collaboration – shared decision-making between researchers and public contributors

11.9 Evaluating the process and impact of PPI

- The *'cube' framework* provides a quick and simple method for evaluating the process of PPI in research based on four key dimensions:
  o Weak voice or strong voice
  o One way to be involved or many ways to be involved
  o Organisation's concerns or public concerns
  o Organisation changes or organisation resists change

- An impact log is a basic way of recording and evaluating the outcomes of PPI in research.

- Information on more comprehensive approaches to planning and executing PPI evaluation is presented in a separate guidance document.

- The GRIPP2 checklists provide useful guidance for reporting PPI in research papers.

GLOSSARY

ADMET studies	Preclinical studies of the bodily absorption, distribution, metabolism, excretion and toxicity of drug candidates to eliminate weak candidates with undesirable properties.
Adverse event/effect	An unfavourable outcome that occurs during or after the use of a medicine or other intervention, but it is not necessarily caused by it.
Advisory group (steering group)	Many research projects have an advisory/steering group to help develop, support, advise and monitor the project. It often includes people who use services, carers, researchers and other health and social care professionals, who can provide relevant advice.
Assay	An investigative (analytic) procedure in laboratory medicine, pharmacology, environmental biology and molecular biology for qualitatively assessing or quantitatively measuring the presence, amount, or functional activity of a target entity. The target entity can be a drug, a biochemical substance, or a cell in an organism or organic sample.
Benefit-risk assessment	In medicines research and development, benefit-risk assessment is the continuous examination of the favourable and unfavourable results of a specific treatment to determine whether its benefits outweigh its risks in a specific condition. It takes into account the evidence on safety and efficacy, as well as other factors like the nature and severity of the condition the medicine is intended to treat or prevent.
Clinical research	Clinical research aims to find out the causes of human illness and how it can be treated or prevented. This type of research is based on examining and observing people with different conditions and sometimes comparing them with healthy people. It can also involve research on samples of blood or other tissues, or tests such as scans or X-rays. Clinical researchers will also sometimes analyse the information in patient records, or the data from health and lifestyle surveys.
Clinical trial or study	Clinical trials are research studies involving human volunteers to compare a new or different type of treatment with the best treatment currently available. They test whether the new or different treatment is safe, effective and any better than what already exists. They are conducted only after a regulatory authority approval and ethics committee review. Clinical trials or studies are often characterised in Phases from I (exploratory) to IV (post-marketing).
CMDh	The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human is a medicines regulatory body representing the EU Member States, Iceland, Liechtenstein and Norway.
Collaboration	Collaboration involves active, on-going partnership with members of the public in the research process. For example, members of the public might take part in an advisory group for a research project, or collaborate with researchers to design, undertake and/or disseminate the results of a research project.
Combinatorial chemistry	A process in drug discovery that involves chemical synthetic methods to generate a large array of structurally diverse compounds, called a chemical or compound library.
Conceptualise	To form an idea or principle in your mind
Consultation	Consultation involves asking members of the public for their views about research, and then using those views to inform decision-making. This consultation can be about any aspect of the research process – from identifying topics for research, through to thinking about the implications of the research findings. Having a better understanding of people's views should lead to better decisions.
Consumer	The term consumer is used to refer collectively to: • people who use services

	• carers • organisations representing consumers' interests • members of the public who are the potential recipients of services
CTTI	Clinical Trials Transformation Initiative is a public-private partnership established by the US FDA and Duke University, North Carolina, to develop and drive adoption of practices that will increase the quality and efficiency of clinical trials.
Dissemination	Dissemination involves communicating the findings of a research project to a wide range of people who might find it useful. This can be done through: • producing reports (often these are made available on the Internet) • publishing articles in journals or newsletters • issuing press releases • giving talks at conferences It is also important to feedback the findings of research to research participants.
EFPIA	The European Federation of Pharmaceutical Industries and Associations represents the pharmaceutical industry operating in Europe.
Eligibility criteria	The key standards that people who want to participate in a clinical study must meet or the characteristics that they must have. These comprise inclusion criteria and exclusion criteria. For example, a study might only accept participants who are above or below certain ages.
EMA	The European Medicines Agency: a body of the European Union which has responsibility for the protection and promotion of public health through the evaluation and supervision of medicines for human use.
ESBLs	Extended-spectrum beta-lactamases are enzymes produced by bacteria such as Escherichia coli (E. coli) and Klebsiella. These bacteria are resistant to many frequently used antibiotics including penicillins and cephalosporins.
EUPATI	The European Patients' Academy on Therapeutic Innovation trains 'patient experts' on medicines development, clinical trials, medicines regulations, and health technology assessment.
Evidence base	An evidence base is a collection of all the research data currently available about a health or social care topic, such as how well a treatment or a service works. This evidence is used by health and social care professionals to make decisions about the services that they provide and what care or treatment to offer people who use services.
FDA	Food and Drug Administration: the Competent Authority in the United States, giving authorisation to conduct clinical trials and issuing marketing licences.
Gantt chart	A visual view of tasks scheduled over time, typically as a horizontal bar chart. Gantt charts are used for planning projects of all sizes and they are a useful way of showing what work is scheduled to be done on a specific day. They also help you view the start and end dates of a project in one simple view.
High throughput screening	A drug discovery process widely used in the pharmaceutical industry to quickly assay the biological or biochemistry activity of a large number of drug-like compounds. It is useful for discovering pharmacological targets.
Hit	A hit is a compound which has the desired activity in a compound screen and whose activity is confirmed upon retesting.
HTA	A Health Technology Assessment produces independent research information about the effectiveness, costs and broader impact of healthcare treatments and tests for those who plan, provide or receive care.

ibid	Means 'in the same source'; used to save space in textual references to a quoted work which has been mentioned in a previous reference.
INVOLVE	A UK national advisory group that supports greater public involvement in the National Health Service (NHS), public health and social care research.
JLA PSPs	James Lind Alliance Priority Setting Partnerships
Lay (lay person)	The term 'lay' means non-professional. In research, it refers to the people who are neither academic researchers nor health or social care professionals.
Lead compound	In drug discovery, this is a chemical compound that has pharmacological or biological activity likely to be therapeutically useful, but may still have suboptimal structure.
Lead optimisation	The drug discovery stage where the chemical structure of the lead compound is used as a starting point for chemical modifications to maintain or improve on desired properties, while reducing known liabilities.
Marketing authorisation	Marketing authorisation (MA) refers to the approval for a medicine to be marketed. A system of MA was put in place to protect public health. MAs are granted only when a competent authority (or 'regulatory authority') has conducted a scientific evaluation, and is satisfied that a medicine is sufficiently safe and effective, and of high enough quality.
Members of the public (or public)	The term is used in this toolkit to include: • past, current, and potential patients • people who use health and social care services • informal (unpaid) carers • parents/guardians • disabled people • potential recipients of health promotion programmes, public health programmes, and social service interventions • organisations that represent people who use services
NDA	The New Drug Application is the vehicle by which drug sponsors formally propose that the Food and Drug Administration (FDA) approve a new pharmaceutical for sale and marketing in the US. In Europe, the Marketing Authorisation Application (MAA) is the NDA equivalent.
NHS	UK's National Health Service
NICE	The National Institute for Health and Clinical Excellence recommends which treatments should be provided by the NHS.
NIHR	The National Institute for Health Research provides the framework through which the Department of Health can position, maintain and manage the research, research staff and research infrastructure of the NHS in England as a national research facility.
Patient centric	An approach where the patient is put first in an open and sustained engagement of the patient, to respectfully and compassionately achieve the best experience and outcome for that person and their family. Important principles for patients are education/information, co-creation, access and transparency.
Person specification	A document that describes the skills, experience, knowledge and other attributes, which an individual must possess to perform the responsibilities of a role.
Pharmacovigilance	The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The European Medicines Agency (EMA) coordinates the European Union (EU) pharmacovigilance system and operates services and processes to support pharmacovigilance in the EU.

PPI	Patient and public involvement: an active partnership between patients and the public and researchers in the research process, rather than the use of people as 'subjects' of research. PPI is often defined as doing research 'with' or 'by' people who use services rather than 'to', 'about' or 'for' them. This includes involvement in the choice of research topics, assisting in the design, advising on the project, or in carrying out the research.
PPIPAD	Patient and Public Involvement Panel for Antimicrobial Drugs, set up by the Department of Medical Microbiology, North Bristol NHS Trust. The name of the panel was determined following a vote by its members.
Preclinical	The stage of research that takes place before any testing in humans is done. Preclinical studies use animals and/or cells or tissues to find out if a medicine, procedure, or treatment is safe and likely to be useful.
Prioritisation	Rigorously examining potential topics for research to identify their importance and where the need for new evidence is greatest.
PRO	Patient-reported outcome: any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.
Protocol/research protocol	A protocol is the plan for a piece of research. It usually includes information about: • what question the research is asking and its importance/relevance • the background and context of the research, including what other research has been done before • how many people will be involved • who can take part • the research method • what will happen to the results and how they will be publicised
Recruitment	Recruitment is the process of enrolling people (participants) into a clinical study. It is based on the inclusion and exclusion criteria that are documented in the protocol.
Role description	A document that describes the general tasks and related responsibilities of a position.
Service user (or user)	A service user is someone who uses or has used health and/or social care services because of illness or disability.
Sponsor	The individual, or organisation (or group of individuals or organisations) that takes on responsibility for confirming that there are proper arrangements in place to initiate, manage and monitor, and finance a study.
Structure-based drug design	A process in drug discovery that involves the design and optimisation of a chemical structure with the goal of identifying a compound suitable for clinical testing i.e. a drug candidate. It is based on knowledge of the drug's three-dimensional structure and how its shape and charge cause it to interact with its biological target, ultimately eliciting a medical effect.
Target validation	The process during drug discovery where the predicted pharmacological target derived from the preceding screening process is verified.
TPP	A Target Product Profile is a document that describes the features of a product (such as a medicine) that a company is planning or developing. The document can include a wide range of information such as dosage, how the product will be administered, formulation, clinical studies, adverse reactions and contraindications.
Trial Management Group (TMG)	The TMG normally includes those individuals responsible for the day-to-day management of the trial, such as the Chief Investigator, statistician, trial manager, research nurse, and data manager. The role of the group is to monitor all aspects of the conduct and progress

of the trial, ensure that the protocol is adhered to, and take appropriate action to safeguard participants and the quality of the trial.

Trial Steering Committee (TSC)	The role of the TSC is to provide overall supervision of the trial. Ideally, it should include members who are independent of the investigators, their employing organisations, funders and sponsors. The TSC should monitor trial progress and conduct, and advise on scientific credibility. It ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.
WEAHSN	The West of England Academic Health Science Network helps to deliver positive healthcare outcomes in the region and nationally by driving the development and adoption of new innovations and enabling patients to play an increasing role in their own care and of others.

APPENDIX 1: Existing work on PPI in medicines development research

Australia

Involving People in Research: A *Consumer and Community Health Research Network* that brings together consumers, community members and researchers to make decisions about health research priorities, policy and practice. It supports the embedding of PPI into standard health research practice and promotes the community 'voice' through their services, resources and training programmes.

Canada

Strategy for Patient-Oriented Research (SPOR): A coalition of federal, provincial and territorial stakeholders dedicated to integrating research into care by involving patients as partners throughout the research continuum, focussing on patient-identified priorities, and improving patient outcomes.

Europe

Innovative Medicines Initiative (IMI): A public-private partnership between the European Union and the international pharmaceutical industry, facilitating open collaboration in research to advance the development of, and accelerate patient access to, personalised medicines for the health and wellbeing of all, especially in areas of unmet medical need. IMI seeks to encourage PPI in all its activities with many projects already involving patients.

European Patients' Academy on Therapeutic Innovation (EUPATI): An IMI-funded project that aims to empower patients and the public to engage more effectively in medicines development research through training courses, educational material and an online public library.

European Medicines Agency (EMA): The agency actively involves patients and consumer groups in scientific discussions on medicines and on the impact of regulatory decisions, to support transparency and improve regulatory processes.

United Kingdom (UK)

INVOLVE: A National Institute for Health Research (NIHR)-funded programme to support active PPI in National Health Service (NHS), public health and social care research.

United States (US) of America

Clinical Trials Transformation Initiative (CTTI): A public-private partnership to develop and drive adoption of practices that will improve the quality and efficiency of clinical trials. CTTI has developed recommendations for effective engagement with patient groups around clinical trials, and a framework to evaluate the financial impact of patient engagement.

Patient-Centered Outcomes Research Institute (PCORI): An independent non-profit, non-governmental organisation established to fund research that can help patients and their carers make better-informed healthcare decisions. PPI is included throughout the research process to ensure the resulting evidence addresses patients' most important questions and concerns.

US FDA: The FDA's Patient-Focused Drug Development (PFDD) initiative is a commitment under the fifth authorisation of the Prescription Drug User Fee Act (PDUFA V) that aims to more systematically gather patient input to help inform understanding of the therapeutic context for medicines development and evaluation. Summaries of the input gathered at each public meeting are published in a series of reports called *The Voice of the Patient*.

International partnership

The **Patient Focused Medicines Development (PFMD)**: An independent non-profit multinational coalition of patients, patient stakeholders and the pharmaceutical industry aiming to co-create and implement a globally standardised meta-framework for PPI in the design and development of research and medicines.

APPENDIX 2: Template expression of interest form

Expression of interest: *[Name of PPI panel]*

Contact Details

Name and title:

Address:

Telephone number: Home: Mobile:

E-mail address:

Preferred method of contact:

How would you prefer to be addressed: First name/Title and surname?

Comments:

Background/Perspective

Were you a: ☐ Service user/patient   ☐ Relative/carer

Broadly, what sort of infection was involved? E.g. respiratory, bone and joint, urological etc.

Were you in intensive care? If so, approximately how long?

Comments:

Availability

What times of day would you prefer for meetings?

What day/time is <u>impossible</u> for you?

Do you require any support to take part?

(E.g. large print written material, wheelchair access to room etc.)

Do you have any dietary requirements?

☐ Yes (please specify):

☐ No

Have you had any involvement with research before, either as a researcher, public panel member or participant?

(Previous experience of research is not a requirement)

Please specify:

Could you summarise briefly why you are interested in joining this panel?

Which of the following are you particularly interested in contributing to?

(Please tick as many as applicable)

☐ Analysing interview data

☐ Literature review

☐ Ethical issues connected with this research

☐ General work of the panel

Thank you for taking the time to join us and for completing this form.

APPENDIX 3: Template letter to responders not selected for a PPI panel

[Organisation logo]

[Address of sender organisation]

[Date]

Dear *[name of recipient]*,

Thank you for your interest in being a member of our *[name of patient panel]*. We have had a very positive response with more people volunteering to participate than we can accommodate. Unfortunately, we are therefore unable to offer you a place on the panel. However, there are other opportunities to become involved in health research. If you would be interested in these, we would be happy to pass your name and contact details to the appropriate people. Please let us know if you would like us to do this.

Thank you once again for your interest in our work.

Yours faithfully,

[Name of sender]
[Job title/role within organisation]

APPENDIX 4: Template impact log for recording outcomes of PPI

[Name of PPI panel] Meetings Impact Log

Date	Attendees/apologies	Discussion	Impact (Outcomes)	Other comments