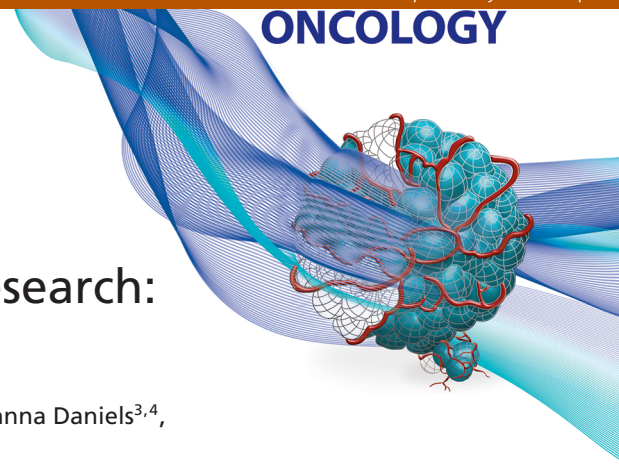
Review

For reprint orders, please contact: reprints@futuremedicine.com



Patient engagement in melanoma research: from bench to bedside

Ann Tivey[1,5], Prerana Huddar[1], Rohan Shotton[1], Imogen Cheese[2,3], Susanna Daniels[3,4], Paul Lorigan[1,5] & Rebecca J Lee*[,1,5]

[1]The Christie NHS Foundation Trust, Wilmslow Road, M20 4BX, UK
[2]Melanoma Patient Conference, Willow Bank, Prince Crescent, Staunton, Gloucestershire, GL19 3RF, UK
[3]Patient Author
[4]Melanoma Focus, Queen Anne House, Gonville Place, Cambridge, CB1 1ND, UK
[5]Division of Cancer Sciences, The University of Manchester, Oxford Road, M13 9PL, UK
*Author for correspondence: Tel.: +44 161 446 3000; Rebecca.lee-3@manchester.ac.uk

Advances in research have transformed the management of melanoma in the past decade. In parallel, patient advocacy has gained traction, and funders are increasingly prioritizing patient and public involvement. Here we discuss the ways in which patients and the public can be engaged in different stages of the research process, from developing, prioritizing and refining the research question to preclinical studies and clinical trials, then finally to ongoing research in the clinic. We discuss the challenges and opportunities that exist at each stage in order to ensure that a representative population of patients and the public contribute to melanoma research both now and in the future.

First draft submitted: 15 November 2020; Accepted for publication: 22 April 2021; Published online: 2 July 2021

Keywords: advocacy • clinical trial • melanoma • patient engagement • PPI • research • risk

In the last decade the clinical and research landscapes of melanoma have perhaps undergone the greatest transformation of all solid malignancies, in a step-change which has been likened to the emergence from the Dark Ages into the Age of Enlightenment [1]. This radical shift in the melanoma treatment paradigm has facilitated many opportunities for patient engagement in clinical decision-making and research.

Patient advocacy in the field of cancer has a rich history that dates back to long before Richard Nixon famously declared a 'war on cancer' in 1971 [2] One of the earliest public collaborations between a patient advocate and a doctor began in 1948, when medical philanthropist, political strategist and health activist Mary Lasker first started corresponding with pediatric pathologist Sidney Farber (often considered the father of modern chemotherapy). Farber described his interactions with Lasker as a 'catharsis', as she was able to co-ordinate their campaign against cancer – an endeavor that required a synergistic partnership [3]. A consequence of widened patient engagement is that there is now a clear imperative for clinicians and researchers to involve patients throughout the research process, from the laboratory bench to translational and clinical studies. This may form a key factor in strengthening patient-centered care over more traditional paternalistic models.

Improving patient involvement in the full process of melanoma research is a challenge for funders, clinicians and scientists. A systematic review of patient and public engagement in cancer research identified that the majority of studies reported involvement preferentially in the earliest stages of the research process, at the expense of the later phases of research [4]. While patients were more likely to be consulted on research prioritization, design and recruitment strategy, few studies involved patients in data generation, processing, interpretation or dissemination. Furthermore, the common challenges and barriers to widening patient engagement were poorly described. These barriers are viewed differently by patients, academics and industry representatives, and the relative value of patient engagement is also viewed differently by the same stakeholders [5]. The well-described barriers to general shared decision-making are also likely to be applicable to patient engagement in research; these may include risk aversion, ambiguity aversion and complex cognitive and emotional interplays [6].

Future Medicine

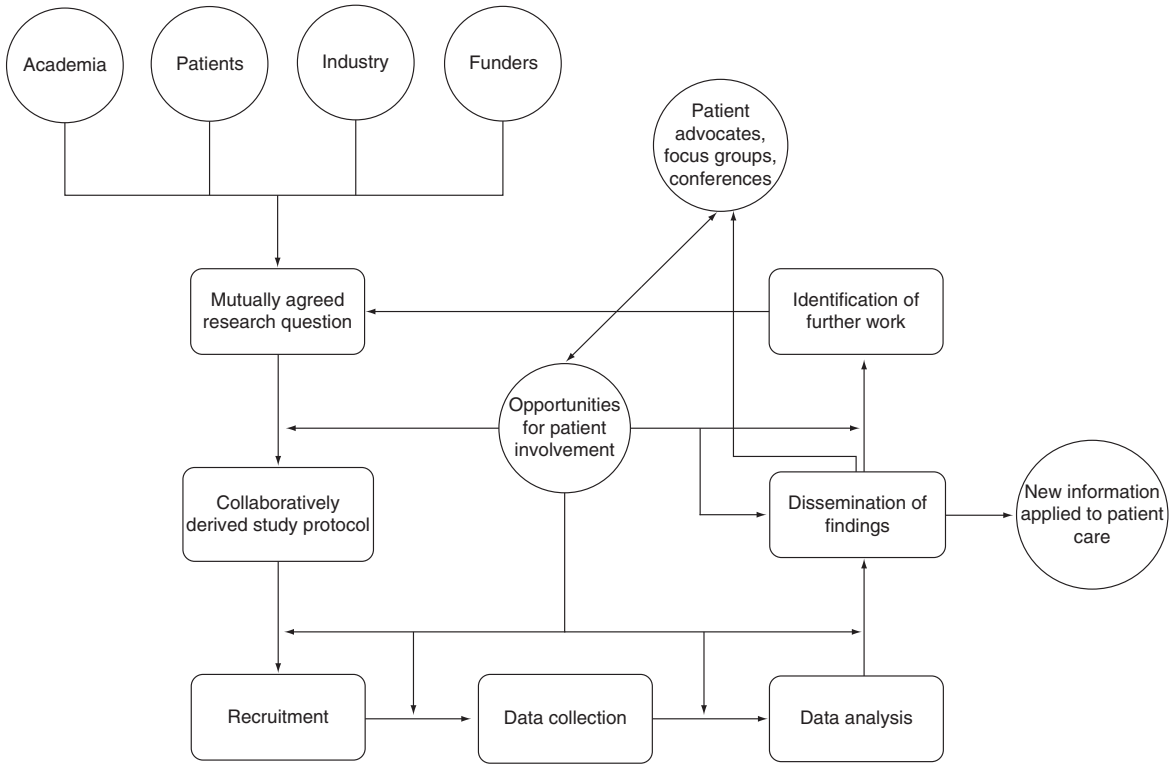


Figure 1. Opportunities for patient and public involvement in melanoma research.

However, opportunities for patient involvement in melanoma research exist at every stage of the research process, as summarized in Figure 1. In this review we discuss the opportunities and barriers to patient engagement in melanoma research in the domains of research question construction, preclinical and translational studies, clinical trials and bringing research findings into the clinic.

Choosing the research question

Patient and public involvement (PPI) and engagement can and should feature in all stages of the research cycle, as emphasized by the National Institute for Health Research (NIHR) Guidelines [7]. This should include the identification, refinement and prioritization of research questions. Often a researcher has an idea about a topic to study, and patients are first involved at the stage of developing that idea into a research proposal for grant applications. Increasingly, the importance of involving patients and carers at an earlier stage in the process is being recognized. This enables questions to be focused on topics that are patient-driven from the very beginning and therefore are more likely to be impactful. It is important to stress that this should be context dependent, as the benefit of patient involvement in some areas will be in developing questions, while in others it will be in refining a question initially posed by researchers.

Many organizations and funding bodies provide support to involve patients in identifying, refining and prioritizing research questions. For example, the James Lind Alliance is a non-profit-making initiative funded by the NIHR that aims to bring patients, carers and clinicians together to determine which areas of 'evidence uncertainties' should be priorities for research attention and funding [8]. It facilitates priority-setting partnerships which aim to identify areas of uncertainty within particular disease areas and prioritize a final 'Top 10′ list that is publicized widely to researchers and funders [9]. These lists can be used as a starting point to develop a research question of relevance to the affected patient population. Patients, carers and clinicians are placed on an equal footing as part of the priority-setting partnerships, giving equal weight to all voices. Funding applications demonstrating how a research proposal would meet one of the Top 10 are more likely to be successful.

There has not been a priority-setting partnership specifically looking for areas of evidence uncertainty in melanoma. This would be a potential opportunity for clinicians, patients and carers to come together to identify and prioritize evidence uncertainties. For example, discussion with patient advocates in the writing of this article

has highlighted how many patients are concerned with the impact of lifestyle factors on their risk of melanoma progression (Cheese I, pers. comm.); these concerns could, for example, refine ongoing research into the impact of the gut microbiome on the efficacy of immunotherapy and how dietary changes may affect this, or work being done on how melanoma patients' BMI relates to overall survival [10,11]. However, there are challenges in adapting researcher-led priorities to patient-led priorities if they do not align, as researchers can have significant emotional investment in the direction of their research and may view changes to that as more risky. Where there is a disconnect between the priorities of researchers, borne from their experiences within the field, and those of individual patient advocates, which are based on their own personal experiences as well as those of others they represent, discussion as to what should be prioritized and why will be important to build understanding of and trust in the research process.

Increasingly, funders are recognizing the importance of involving patients in developing funding calls. A large-scale example of this is the Cancer Research UK (CRUK) 2015 Grand Challenge, which used patient and carer involvement throughout to develop and refine seven specific key questions [12]. This included workshop events called 'Big Thinks', held across the country with large numbers of patients and smaller regular patient panels. Here researchers are in dialogue with patients, enabling big research questions to be discussed and refined in order to make them relevant to the priorities of patients and the public. Subsequently, CRUK has partnered with the National Cancer Institute to jointly fund Cancer Grand Challenges for large-scale, international multidisciplinary projects [13]. The NIHR includes members of the public or 'advocates' in its funding committees to decide both on funding individual research projects and on determining research priorities that will feed into funding calls. On a simpler level, there is an easily accessible online form on the NIHR's website for anybody to submit research questions or topics they think the NIHR should support.

Since 2019, the USA-based Melanoma Research Foundation has included a patient review panel as part of its grant proposal process that ensures representation of the patient's perspective on allocation of resources to research [14]. AIM at Melanoma Foundation, another USA-based organization, founded the Women in Melanoma Conference in 2017 in recognition of the need to address 'new' topics such as treatment effects on fertility and the prolonged anxiety of living with advanced melanoma for many years – topics which were not previously a research focus [15]. This event aims to bring female researchers and patients together to develop collaborations, with AIM at Melanoma providing funding and support to projects arising from the meeting. These initiatives aid dialogue between patients and researchers in order to synthesize questions that are relevant and important to both parties.

A circular challenge is the necessity of having PPI to gain funding, while high-quality PPI itself requires financial investment. Building PPI into the earliest stage of designing the research question, prior to obtaining substantive grant funding, can often be constrained by the cost implications. In recognition of this, a number of funding opportunities for PPI are available. Often universities are able to provide small grants to support such work. The NIHR offers grants of up to £1000 to support PPI work through its research design services and PPI Small Grants scheme [16]. These grants can be used to publicize engagement events to diverse audiences and cover travel expenses and refreshments, ensuring that the widest possible range of patients and carers have the opportunity to be involved. Ensuring diversity in terms of both patient and carer views is important given the impact of melanoma management on not just the patient but their relatives and care providers. Direct payment to patients for time given is unusual, but patients have also highlighted the importance of being informed of the progress of the research and being made to feel their contributions are recognized and valued.

Preclinical research

Preclinical research, especially basic research, has not traditionally been an area that has involved PPI. However, increasing dialogue and discussions can help to crystallize questions and thoughts as well as to prioritize objectives. In addition, this increased involvement has been shown to reduce research waste through prioritization of studies that are likely to benefit human health the most, which is particularly important when charitable donations are used to fund the work [17]. A study examined the challenges reported by researchers, which included concerns about time commitment, ability to communicate (especially with patients who may have a terminal diagnosis) and public judgement of ethically approved research (particularly animal experimentation) [18]. This demonstrates some of the less obvious barriers to PPI previously mentioned: researchers' own emotional relationship to their work and fear of their work being misunderstood or misrepresented. These may be particularly pertinent in the preclinical phase, where researchers do not necessarily have a clinical background and the link between their work and patient benefit may seem less direct. Based on this study, the authors developed a PPI assessment survey, which could be used by

researchers to assess and refine their PPI [18]. CRUK has also developed a toolkit for researchers with guidance, case studies and templates to aid researchers in planning, delivering and evaluating patient involvement [19].

It is important not only to provide guidance to researchers, but also to train and educate patient advocates so they can understand research processes in order to promote dialogue. The Cancer Survivor and Patient Advocacy Program set up in 2004 by the American Association of Cancer Research is an example of the way in which organizations can engage patients and educate through lectures in lay language as well as enabling advocacy [20]. The Melanoma Patient Network Europe runs workshops that tutor patient advocates on relevant translational research topics (e.g., the 2020 workshop focused on genomics and transcriptomics) and how these technologies are being used in melanoma research [21]. In this way, patient and scientist partnerships can be facilitated through better communication and direct contact.

Patients and the public can be involved in basic research in a number of ways. Many institutions are now offering laboratory tours where researchers can talk directly to the public about their work. In addition, larger institutions such as the Francis Crick Institute have public exhibition spaces, which can be used to educate regarding ongoing work [22]. A more novel example of engagement in basic science is a cancer-themed escape room exploring malignancy and metastasis [23]. Being creative in explaining research to the public can help to involve them in the research process and may inspire scientists of the future. Explaining findings and ongoing research to the public is an important aspect of engagement; however, involving the public more directly in research can further increase its quality. The NIHR INVOLVE initiative has developed a set of national UK standards and tips which are relevant to researchers internationally in framing interactions with the patients and the public throughout the research process, from grant reviews to meetings [7]. There are many other frameworks which can be used to aid PPI engagement in research. A systematic review revealed that there are five main types – power-focused, priority-setting, study-focused, report-focused and partnership-focused – however, they are rarely used by those outside the groups that designed them [24]. Thus it recommended that researchers personalize their own toolkit based on the work of others and developed a set of resources for an evidence-based 'develop your own framework' workshop, which could be used by researchers in partnership with patients and the public [24].

In developing translational research programs, patient input is critical to success. Many of these programs require patient samples to test hypotheses and to validate laboratory findings. Some samples, such as biopsies, are more invasive than others and this requires careful discussion regarding risks and benefits to the patient. Here patient involvement is crucial to optimize sample collection, especially in terms of information sheets and consent. Often there is an additional optional consent for the use of translational samples taken during clinical trials. Although much work has been done on understanding barriers to consent for participation in trials, there are few publications understanding patient decision-making with regards to consent for additional research samples. One study looking at factors influencing patients' consent to biobanking found that support was high (93%) [25]. Ongoing PPI throughout the life of a study may be able to address any patient concerns with obtaining samples for translational research, ensuring optimal collections are achieved.

Clinical trials

Trial design

PPI in clinical trial design is increasing, particularly where studies are investigator led; however, the degree to which trial designs are influenced by PPI is highly variable. One of the key challenges is to embed PPI into trials developed by large pharmaceutical companies, as this is an area where there is historically little contribution. Although a requirement for PPI in order to obtain grant funding has supported an expansion of the role it plays in academic studies, trials sponsored by industry are not subject to the same financial levers. This has likely resulted in decreased involvement of patients in both design and management of pharma-led studies compared with investigator-led studies. The NIHR is trying to bridge this gap with its Patient Engagement in Clinical Development Service, which aims to bring patients and industry together in order to develop 'patient-friendly' protocols. However, involving patients in the process of trial conception and design provides multiple benefits to both academic and industry sponsored trials.

Many studies have shown that when considering therapeutic options, patients consistently prefer drugs that provide a good quality of life with minimal side effects and the extension of overall survival [26,27]. Unfortunately, research has shown that these preferences are commonly overlooked, especially when accelerated approvals are sought [28]. Many clinical trials and drug approval committees use surrogate end points such as progression-free survival in lieu of end points, such as overall survival and quality of life (QoL), which are shown to be patient

priorities [29]. A study examining the use of QoL data in regulatory approvals found that few indications met defined criteria for clinically meaningful improvement in QoL [30]. One of the reasons may be the lack of standardization in these measures, which makes comparisons across trials difficult and may cause regulatory authorities to place less emphasis on their applicability to the approvals process [30,31]. Lack of standardization may also result in data being at more risk of ambiguity. This does appear to be changing with the creation of the Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints (SISAQoL) data initiative and the release of new guidance by the US FDA on the collection and interpretation of patient experience data [31–33]. PPI will be key to ensuring these initiatives are successful.

Another reason may be that QoL assessments can be challenging to interpret. For example, the Phase III EORTC 18071 trial of adjuvant ipilimumab versus placebo in stage III resected melanoma showed no clinically relevant overall impairment of global health/quality of life, as measured by the European Organisation for Research and Treatment of Cancer questionnaire QLQ-C30, between the treatment and the placebo arms; however, adverse events led to treatment discontinuation in 52% of patients receiving ipilimumab [34,35]. The on-treatment assessment time point was too early for the results to have been influenced by disease relapse; thus there appears to be a discrepancy between the reported QoL and the significant side effects experienced. Whether this was due to the types of questions asked or the timing of assessments is unclear [36], but this highlights some of the challenges in assessing QoL. Use of electronic devices may aid the timing of assessments, and discussion with patient representatives may also help to optimize how QoL measurements are undertaken. Engagement with carers when designing QoL tools may offer an additional perspective in terms of factors they have identified as impacting on the patient's well-being and functional abilities. Clearly, in order to focus on the stated patient priorities of QoL and overall survival, research is required to examine the best approaches to obtaining interpretable and clinically relevant data.

There are examples of the way in which PPI has supported the successful development of clinical trials. CRUK has a selection of patient case studies providing perspectives of patient involvement in various clinical trials [19]. For example, the PRIMETIME trial (examining postoperative avoidance of radiotherapy) is investigating biomarker-directed radiotherapy in breast cancer [37]. PPI was instrumental to the trial's design and research application, as well as driving recruitment to the study. Initially, the study investigators had planned a single-cohort study design to test whether radiotherapy could be avoided in patients with low risk of local recurrence. However, this failed to attract the requisite funding. The patient advocates argued strongly that a patient's decision to join a study such as PRIMETIME depended on their perception of risk and that this was particularly difficult when levels of risk and benefit were low. They proposed that the investigators should instead develop a biomarker-directed study to direct the use of radiotherapy, in order to better define which patients were at higher risk of local recurrence. This early revision of the study design led to a successful application for funding from CRUK. The patient advocates also played a key role in the ethics submissions, patient information leaflet design and in driving recruitment. Thus the PRIMETIME trial is a useful case study of how PPI can play an influential role in clinical research, throughout all stages of the study process.

Our own DETECTION study in melanoma (DETECTION EudraCT 2020-000234-17), is examining whether early treatment based on the detection of ctDNA in patients with resected stage IIB/C melanoma improves survival [Lee R, unpublished data]. When designing it, we performed a number of focus groups with public and patients to gauge the acceptability of blinding patients in the standard-of-care arm to their ctDNA result, which would prevent bias. Support for the design was encouraging; patients were happy to view it as a form of 'placebo' as long as standard-of-care follow-up procedures were followed. Through PPI, we were able to explain clearly in the patient information sheet the rationale for the trial design. A further example of successful PPI is a study conducted in 2019 assessing the effectiveness of a guideline-based colony stimulating factor standing order intervention, which went even further than traditional patient engagement activities by including patient groups as major stakeholders during early trial development. The patients were then included as co-authors on subsequent publications and presentations. Annual satisfaction survey results showed that all stakeholders were satisfied with the communication process and the methodology of the trial itself [38].

In order to enhance the role of patient advocates as increasingly important members of the research team, it is important to give them the tools with which they can interpret the clinical and preclinical data given to them. There are growing efforts across the world to involve patients in clinical research and the dissemination of published results across all disciplines [39]. Melchior *et al.* described a palliative care initiative in The Netherlands in which they trained patients and lay members of the public to prepare them for participation in research [40]. The investigators found that

due to this training program, their project aims became more relevant to the intended audience. In the USA, a novel framework has been developed and piloted to engage patients in cancer trials networks [41]. An interesting aspect of this framework was the initiative to design training courses for patient advocates, which would empower them to make meaningful contributions to study design. There was also a framework for researcher–advocate engagement, which allowed for bidirectional learning. In a similar vein, the American Society of Clinical Oncology recently introduced a membership for patient advocates which includes access to their international meetings. This aims to provide patient advocates with the skills, resources and opportunities they need to perform their roles effectively in developing research and engaging fellow patients. As discussed above, the Melanoma Patients Network Europe holds regular workshops to support patients and carers to understand the research process and be better equipped to advocate effectively within it.

Trial delivery & recruitment

Equitable access to trials enables all patients to potentially benefit from access to new treatments and is critical to their relevance for real-world patient populations. Furthermore, patient recruitment is extremely important in delivering trials in a timely manner in order to bring new therapies to the clinic as soon as possible. A study examining ways in which recruitment and retention of participants could be improved identified a number of strategies, including personalized thank you notes, ensuring regular communication through the use of websites and flyers, and ensuring physicians remain up to date with the study in order to maintain patients' trust that their treating clinicians are knowledgeable about the trial [42]. Similarly, as participation in clinical trials can also have a huge impact on carers, it is important they are included in strategies to enable patient access [43]. One of the key aspects in driving a large randomized controlled trial is to ensure that its existence is highlighted to potential participants. This can be mutually beneficial: patients may have more treatment options available to them through the trial, and researchers are able to improve recruitment. To address this, Aim at Melanoma has a trials finder available for patients in the USA [44] and Melanoma Focus is developing a similar tool for UK patients which enables them to easily find potential trials to discuss with their clinician. The NIHR also has a broader trials finder for cancer patients independent of tumor type [45]. These are important tools that can connect researchers with patients, aiding the research process as a whole.

In addition to improving access to trials, better patient engagement in the process of trial design could improve diversity in the populations of patients recruited. A 2018 review investigating the representation of women and minority ethnic groups in cancer clinical trials conducted a subgroup analysis showing that only 35% of melanoma patients on trials were women, while 49% of melanoma cases in the UK occur in women [46,47]. Similarly, a study investigating trial participation among young women with melanoma, lymphoma, breast cancer, thyroid cancers or gynecological malignancies revealed that 76% of patients had never discussed a clinic trial with their treating team despite trials being available, and only 5% had taken part in a trial [48]. Better strategies are needed to involve these historically under-represented groups in all stages of trial design, thereby improving diversity of patients recruited into trials.

Trial recruitment & informed consent

Although some studies have investigated patient barriers to participation in clinical research, there are few studies examining how trials are communicated to patients and how to broach complex topics such as clinical trial participation. Fear of side effects, reduced QoL and receiving ineffective treatment were cited as three of the most common barriers to clinical trial participation in a large meta-analysis [49]. Another study examined how different ways of discussing a trial can affect the likelihood of a patient consenting to participation [50]. One study explored the issues of communication and informed consent in Phase 1 trials and emphasized that this group of patients are often vulnerable and are at risk of not understanding the rationale and aims of trials [51]. The authors found that there can be an unrealistic expectation of the benefits and risks associated with trial participation and highlighted the need for open and frequent communication [51]. Thus there is a huge opportunity for PPI to identify the best ways of communicating a trial to patients, ensuring that risks and benefits are appropriately discussed. Once identified, these need to be effectively communicated to all physicians working on the trial in order to support their discussions.

Disseminating research results to patients

One of the key aspects of ensuring patients remain engaged and motivated to participate in the research process is to communicate updates and results from studies. However, one study found that fewer than half of researchers had disseminated or planned to disseminate results to patients and that only half of those were going to using lay language in their dissemination [52]. Reported barriers to disseminating results included researchers' opinions that the results would not be interesting to patients, lack of time, difficulties in reaching patients, lack of early planning (which meant they were unable to contact the patients) and lack of perceived incentives [52]. PPI at earlier stages in the research process may help with planning for results to be disseminated in ways that are accessible to patients and the public. In addition, funders could both incentivize this process and provide support in disseminating results through their websites and media outlets. For example, since 2009 CRUK has published plain English summaries of trials results and currently has over 50 published summaries for melanoma trials [53].

An EU Clinical Trials regulation introduced in 2014 and set to be fully implemented in 2021 mandates publication of a lay summary within a year of the end of a trial [54]. As with the role of patients, carers and the public in supporting development of accessible and comprehensible trial literature, involving these groups in the development of lay summaries has been successfully used to enhance their value to the intended audience [55]. This will enable better-quality summaries to be produced which not only fulfill regulatory obligations but also provide useful information to patients. Finally, existing events and platforms led by patient advocacy groups, such as the Melanoma Patient Conference held in the UK or the Melanoma Patient Network Europe Conference, could be used to disseminate findings to audiences wider than those reached by traditional scientific congresses.

In the clinic

As patient experience has dramatically diversified in the 21st century, so too has the possibility of more nuanced patient choice and involvement in clinical decision-making. Over the past decades in medicine, there has been a trend toward a less paternalistic model of medicine in which the patient's agenda is at the forefront of the consultation and shared decisions occur. This approach is thought to lead to improved patient understanding and better overall health outcomes [56]. However, lack of understanding of statistical concepts such as absolute and relative risk, even among doctors, can result in poor communication of trial results [57]. The authors of one study argued that poor presentation of the statistics to patients can lead to them making poor decisions about their treatment [57]. They proposed that instead of focusing discussions on relative risk reductions (which can mislead both clinicians and patients to overestimate the benefit of a proposed treatment), clinicians should represent the same statistical information in the form of conditional probabilities, natural frequencies or numbers needed to treat. Pictures and graphs could further aid the discussion and foster insight. In addition, they recommended that clinicians be conscious of using balanced language in order not to inadvertently sway the patient in a particular direction [57].

To aid such discussions, Melanoma Focus has developed a 'Melanoma Patient Decision Aid' in the form of an interactive web page that details the diagnostic, treatment and follow-up algorithms for each stage of cutaneous melanoma [58]. Furthermore, Melanoma Institute Australia has a publicly available open-access risk calculator that is intended as a tool to help guide discussions regarding adjuvant therapy between patients and clinicians [59]. It is critical, once research has been conducted and reported, that patients have an understanding of the proposed benefits of treatment and any short- or long-term side effects that could result from it.

However, research does not stop once drugs are brought to the clinic; there are many follow-on questions which need to be addressed. The use of new technologies, including social media, opens a potentially less onerous path for patient engagement in clinical research for both patients and the research team outside of the formal setting of a clinical trial. An Australian study investigating exercise behaviors and fatigue in patients receiving immunotherapy for advanced melanoma utilized a survey on a social media group for melanoma patients and their families/carers [60]. The survey collected 55 responses from approximately 200 eligible patients with just three posts of the survey link by the research team. 'My Melanoma' is an app that is currently in development, spearheaded by patient advocates. It is intended to include the patient themselves as a researcher; the app will enable patients to enter details of their diagnosis, past medical history and treatment [61]. The patient will also be asked whether they would consent to their tissue samples being used in future research projects. This app will also allow for contemporaneous and prospective data collection, as patients can upload data about their symptoms and disease course in real time. It is important, however, to ensure transparency and security of data so that patients feel comfortable to engage with it.

This is a novel and innovative approach to empower the patient population and engage them as active members of the research community throughout their treatment journey.

Discussion

Patient engagement is important throughout all stages of the research cycle. Increasingly, it is becoming a collaborative exercise in which patients are seen as partners in developing/refining research questions, designing clinical trials and helping to translate research findings into changes in clinical practice. We are in the midst of an exciting era in melanoma research, and patients have the potential to shape the future of it in alliance with research teams and clinicians. In this review we have discussed how patients and the public can be engaged at every step of the research process, from developing a question, preclinical research and clinical trial design to ongoing research in the clinic. However, it is important not to turn this into a tokenistic exercise, so it remains a fruitful endeavor for patients, scientists, clinicians and other members of the research team [62]. Dialogue between different stakeholders, including researchers and patients, is extremely important if the public is to trust the research process and its outputs.

In order to widen PPI engagement, clinicians and scientists may access patient input via individual patient advocates, patient focus groups and wider patient conferences. Because it is a malignancy with a relatively high incidence in younger adults [63], patients with melanoma may be more comfortable using social media platforms than patients with some other tumors. Prominent individual advocates may garner many followers via blogs and social media channels and feed into large-scale meetings such as the Melanoma Patient Conference [64]. While there are growing opportunities offered by social media and technology to engage with a wider range of patients, there remain challenges in ensuring patient engagement effectively represents the population to which the research pertains.

The patients who are most involved with PPI and melanoma-focused social media posts are inevitably biased toward a more educated, engaged and informed patient group that may not reflect the melanoma patient population as a whole. This means that, for example, when working with patients to develop patient information sheets, it is important that the language is accessible for the average reading age of the patient population and not necessarily merely for those patient advocates who have had training in clinical trial design. This is where finding novel ways to reach a wide range of patients is particularly important. A challenge throughout all areas of research is finding ways to reach patients who have not actively sought out opportunities to participate in patient engagement events. Adequately recompensing patients for the time and expenses associated with their involvement in PPI activities is important to ensure people are not excluded for economic reasons (INVOLVE 2012 PPI guidelines) [65]. Consideration of practical aspects, such as ensuring events take place at places convenient for those reliant on public transport and at times outside of working hours, can broaden the reach of PPI activities. The rise of online events such as virtual focus groups brought about by the COVID-19 pandemic offers opportunities and may lessen the financial, logistical and geographical barriers to involvement. As a consequence of the pandemic, more people have gained confidence with digital technologies, which will increase the potential for participation in social media and app-based patient involvement programs. In addition, the pandemic accelerated the use of telemedicine both in the clinic and within trials, but with limited evaluation of its impact on patient satisfaction. Going forward, if telemedicine is incorporated into the design of new trials, it will be important to engage with patients to ensure technology is used in ways that does not compromise their experience. Furthermore, virtual events must still be developed with consideration for patients who are less confident with use of this technology in order to be truly inclusive.

While linking funding to PPI is an important motivator to engage researchers in the process, it is important that PPI is recognized for the ways in which it enhances research in its own right. These include prioritization of research questions in order for them to have the most impact and improving accessibility of clinical trials to patients (and thereby recruitment) through input into trial design and patient-facing literature. In this way the precious resources of patient data, samples and funding can be utilized the most effectively.

Future perspective

The value of patient and public engagement in the research process is gaining increasing recognition. PPI input can inform every stage, from developing the research question to obtaining real-world data and patient samples in the clinic. Critically, as novel ways to treat melanoma increase, so does patient choice; therefore it is important not only to engage patients in developing research but also to ensure that findings are explained fully to them so they can make informed treatment choices.

Novel methods of engaging patients and the public will be important for the future of PPI, especially in terms of increasing diversity. Technology will have a significant role in enabling interactions between researchers and the public. Digital applications can not only obtain data, but also help to retain interest and disseminate results to patients. Only by working together with patients and the public can we can build on the past decade of advancements to continue to improve the lives of patients with melanoma.

Executive summary

Developing & refining the research question

- Patients and researchers can be partners in developing, refining and prioritizing a research question or strategy.
- Opportunities for patient involvement in melanoma research exist at every stage of the research process.
- Barriers to general shared decision-making – such as risk aversion, ambiguity aversion and complex cognitive and emotional interplays – are also likely to be applicable to patient engagement in research.
- Patient and public involvement (PPI) and engagement can and should feature in all stages of the research cycle, as emphasized by the National Institute for Health Research and EMA guidelines.
- Funders are increasingly recognizing the importance of involving patients in developing funding calls.

Preclinical research

- Preclinical research, especially basic research, has not traditionally been an area that has involved PPI.
- The use of PPI has been shown to reduce research waste through prioritization of studies that are likely to benefit human health the most.
- Many frameworks and opportunities exist for scientists to interact and engage with patients and the public – the key is to tailor the engagement to individual programs of work.

Clinical trials

- Patient and public engagement is critical to enable optimal trial design that appeals to potential participants, to inform consent and to aid recruitment strategies.
- Patient priorities for end points in clinical research include quality of life and overall survival.
- There are many examples of how PPI has improved trial design.

In the clinic

- Equitable access to trials enables all patients to potentially benefit from access to new treatments and is critical to the trials' relevance to real-world patient populations.
- It is important to communicate research results clearly to patients in the clinic in order for informed decision-making to occur.

Challenges & future directions

- The key challenge is to enable broad patient and public engagement in order for the data obtained to be representative of the real population.
- Dissemination of results is important to maintain engagement.
- Social media and online platforms will increasingly aid dialogue between researchers and patients.
- The restrictions on face-to-face interactions during the COVID-19 pandemic give an important opportunity to enhance engagement with patients using virtual platforms.

Financial & competing interests disclosure

R Lee is supported by the National Institute for Health Research as a clinical lecturer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as: • of interest

1. Albertini MR. The age of enlightenment in melanoma immunotherapy. *J. Immunother. Cancer* 6(1), 80 (2018).
2. Perlmutter J, Bell SK, Darien G. Cancer research advocacy: past, present, and future. *Cancer Res.* 73(15), 4611–4615 (2013).
3. Mukherjee S. *The Emperor of All Maladies: A Biography of Cancer.* Scribner, New York, USA (2010).
4. Pii KH, Schou LH, Piil K, Jarden M. Current trends in patient and public involvement in cancer research: a systematic review. *Health Expect.* 22(1), 3–20 (2019).
5. Smith SK, Selig W, Harker M *et al.* Patient engagement practices in clinical research among patient groups, industry, and academia in the United States: a survey. *PLoS ONE* 10(10), e0140232 (2015).
6. Reyna VF, Nelson WL, Han PK, Pignone MP. Decision making and cancer. *Am. Psychol.* 70(2), 105–118 (2015).

7. National Institute for Health Research. UK Standards for Public Involvement – INVOLVE (2012). www.invo.org.uk/posttypepublication/uk-standards-for-public-involvement-v6/
8. National Institute for Health Research. About the James Lind Alliance (2020). www.jla.nihr.ac.uk/about-the-james-lind-alliance/
- **Provides information about the James Lind Alliance, which provides support for patient involvement in priority setting rather than patients being involved after a research question has already been determined.**
9. James Lind Alliance. UK Top 10 living with and beyond cancer research priorities (2018). www.ncri.org.uk/areas-of-interest/living-with-beyond-cancer/
10. Gopalakrishnan V, Helmink BA, Spencer CN, Reuben A, Wargo JA. The influence of the gut microbiome on cancer, immunity, and cancer immunotherapy. *Cancer Cell* 33(4), 570–580 (2018).
11. McQuade JL, Daniel CR, Hess KR *et al.* Association of body-mass index and outcomes in patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy: a retrospective, multicohort analysis. *Lancet Oncol.* 19(3), 310–322 (2018).
12. Cancer Research UK. Cancer grand challenges: about (2015). www.cancerresearchuk.org/funding-for-researchers/cancer-grand-challenges
13. National Cancer Institute. Cancer grand challenges. www.cancer.gov/grants-training/grants-funding/cancer-grand-challenges
14. Melanoma Research Foundation. Learn about grant reviews (2019). https://melanoma.org/research-science/participate-in-science/learn-about-grant-reviews/
15. AIM at Melanoma Foundation. Women in melanoma: AIM's latest success story (2019). www.aimatmelanoma.org/women-in-melanoma-wim/
16. National Institute for Health Research. Learn about the small grants scheme (2020). www.nihr.ac.uk/health-and-care-professionals/engagement-and-participation-in-research/learn-about-the-small-grants-scheme.htm
17. Chalmers I, Bracken MB, Djulbegovic B *et al.* How to increase value and reduce waste when research priorities are set. *Lancet* 383(9912), 156–165 (2014).
18. Maccarthy J, Guerin S, Wilson AG, Dorris ER. Facilitating public and patient involvement in basic and preclinical health research. *PLoS ONE* 14(5), e0216600 (2019).
19. Cancer Research UK. Patient involvement toolkit for researchers (2020). www.cancerresearchuk.org/funding-for-researchers/patient-involvement-toolkit-for-researchers
20. American Association for Cancer Research. Patient advocacy. www.aacr.org/patients-caregivers/patient-advocacy/
21. Melanoma Patient Network Europe. MPNEhubs workshop Krusenberg 2020. (2020). http://www.melanomapatientnetworkeu.org/krusenberg-2019.html
22. The Francis Crick Institute. Engage and inspire the public (2020). www.crick.ac.uk/about-us/our-vision/engage-and-inspire-the-public
23. Excite Science. Cancer Puzzle Room (2020). www.excitescience.org/cancerpuzzleroom
24. Greenhalgh T, Hinton L, Finlay T *et al.* Frameworks for supporting patient and public involvement in research: systematic review and co-design pilot. *Health Expect.* 22(4), 785–801 (2019).
25. Pillai U, Phillips K, Wilkins G *et al.* Factors that may influence the willingness of cancer patients to consent for biobanking. *Biopreserv. Biobank.* 12(6), 409–414 (2014).
26. Khan FA, Akhtar SS, Sheikh MK. Cancer treatment – objectives and quality of life issues. *Malaysian J. Med. Sci.* 12(1), 3–5 (2005).
27. Meropol NJ, Egleston BL, Buzaglo JS *et al.* Cancer patient preferences for quality and length of life. *Cancer* 113(12), 3459–3466 (2008).
28. Prasad VK. *Malignant: How Bad Policy and Bad Evidence Harm People with Cancer* (1st Edition). Johns Hopkins University Press, (2020).
29. Gyawali B, Hwang TJ, Vokinger KN, Booth CM, Amir E, Tibau A. Patient-centered cancer drug development: clinical trials, regulatory approval, and value assessment. *Am. Soc. Clin. Oncol. Educ. B* (39), 374–387 (2019).
30. Arciero V, Delos Santos S, Koshy L *et al.* Assessment of Food and Drug Administration- and European Medicines Agency-approved systemic oncology therapies and clinically meaningful improvements in quality of life: a systematic review. *JAMA Netw. Open* 4(2), e2033004 (2021).
31. Bottomley A, Pe M, Sloan J *et al.* Analysing data from patient-reported outcome and quality of life endpoints for cancer clinical trials: a start in setting international standards. *Lancet Oncol.* 17(11), e510–e514 (2016).
32. US Food and Drug Administration. Patient-focused drug development: methods to identify what is important to patients guidance for industry, food and drug administration staff, and other stakeholders. www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-methods-identify-what-important-patients-guidance-industry-food-and
33. US Food and Drug Administration. Patient-focused drug development: collecting comprehensive and representative input. www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-collecting-comprehensive-and-representative-input

34. Coens C, Suciu S, Chiarion-Sileni V *et al.* Health-related quality of life with adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): secondary outcomes of a multinational, randomised, double-blind, Phase 3 trial. *Lancet Oncol.* 18(3), 393–403 (2017).

35. Eggermont AMM, Chiarion-Sileni V, Grob JJ *et al.* Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, Phase 3 trial. *Lancet Oncol.* 16(5), 522–530 (2015).

36. Lorigan P, Green AC. Immunotherapy: does adjuvant ipilimumab have little adverse effect on quality of life? *Nat. Rev. Clin. Oncol.* 14(7), 395–396 (2017).

37. Kirwan CC, Coles YCE, Bliss J. It's PRIMETIME. Postoperative avoidance of radiotherapy: biomarker selection of women at very low risk of local recurrence on behalf of the PRIMETIME Protocol Working Group. 2: Side-effects from breast radiotherapy may now outweigh potential benefit in some patients. *Clin. Oncol.* 28, 594–596 (2016).

38. Barger S, Sullivan SD, Bell-Brown A *et al.* Effective stakeholder engagement: design and implementation of a clinical trial (SWOG S1415CD) to improve cancer care. *BMC Med. Res. Methodol.* 19(1), 119 (2019).

39. Arnstein L, Wadsworth AC, Wadsworth AC *et al.* Patient involvement in preparing health research peer-reviewed publications or results summaries: a systematic review and evidence-based recommendations. *Res. Involv. Engagem.* 6(1), 34–34 (2020).

40. Melchior I, Heijden A, Stoffers E, Suntjens F, Moser A. Patient and public involvement cultures and the perceived impact in the vulnerable context of palliative care: a qualitative study. *Heal. Expect.* DOI: 10.1111/hex.13186 (Online ahead of print) (2021).

41. Deverka PA, Bangs R, Kreizenbeck K *et al.* A new framework for patient engagement in cancer clinical trials cooperative group studies. *J. Natl Cancer Inst.* 110(6), 553–559 (2018).

- **Describes a structured framework to engage patient advocates more effectively in the development of cancer clinical trials that the authors intend will provide a roadmap for other clinical trials groups looking to more effectively bring the patient voice into trial conception and design.**

42. Chhatre S, Jefferson A, Cook R *et al.* Patient-centered recruitment and retention for a randomized controlled study. *Trials* 19(1), 205 (2018).

43. Witteman HO, Chipenda Dansokho S, Colquhoun H *et al.* Twelve lessons learned for effective research partnerships between patients, caregivers, clinicians, academic researchers, and other stakeholders. *J. Gen. Intern. Med.* 33(4), 558–562 (2018).

44. AIM at Melanoma Foundation. Aim At Melanoma clinical trial matching service (2020). https://app.emergingmed.com/aim/home/

45. National Institute for Health Research. Be part of research. https://bepartofresearch.nihr.ac.uk/

46. Duma N, Aguilera JV, Paludo J *et al.* Representation of minorities and women in oncology clinical trials: review of the past 14 years. *J. Oncol. Pract.* 14(1), e1–e10 (2018).

47. Cancer Research UK. Melanoma skin cancer incidence statistics. (2020). https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/melanoma-skin-cancer#:~:text=Melanoma%20skin%20cancer%20risk&text=1%20in%2036%20UK%20males,in%20the%20UK%20are%20preventable

48. Anderson C, Smitherman AB, Meernik C *et al.* Patient/provider discussions about clinical trial participation and reasons for nonparticipation among adolescent and young adult women with cancer. *J. Adolesc. Young Adult Oncol.* 9(1), 41–46 (2020).

49. Mills EJ, Seely D, Rachlis B *et al.* Barriers to participation in clinical trials of cancer: a meta-analysis and systematic review of patient-reported factors. *Lancet Oncol.* 7(2), 141–148 (2006).

50. Albrecht TL, Eggly SS, Gleason MEJ *et al.* Influence of clinical communication on patients' decision making on participation in clinical trials. *J. Clin. Oncol.* 26(16), 2666–2673 (2008).

51. Cox AC, Fallowfield LJ, Jenkins VA. Communication and informed consent in Phase 1 trials: a review of the literature. *Support. Care Cancer* 14(4), 303–309 (2006).

52. Schroter S, Price A, Malički M, Richards T, Clarke M. Frequency and format of clinical trial results dissemination to patients: a survey of authors of trials indexed in PubMed. *BMJ Open* 9(10), 32701 (2019).

53. Cancer Research UK. Trial search results. www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/clinical-trials-search?populate=Melanoma&f%5B0%5D=field_trial_status%3A4396

54. Barnes A, Patrick S. Lay summaries of clinical study results: an overview. *Pharmaceut. Med.* 33(4), 261–268 (2019).

55. Raynor DK, Myers L, Blackwell K, Kress B, Dubost A, Joos A. Clinical trial results summary for laypersons: a user testing study. *Ther. Innov. Regul. Sci.* 52(5), 606–628 (2018).

56. Elwyn G, Frosch D, Thomson R *et al.* Shared decision making: a model for clinical practice. *J. Gen. Intern. Med.* 27(10), 1361–1367 (2012).

57. Gigerenzer G, Edwards A. Simple tools for understanding risks: from innumeracy to insight. *BMJ* 327(7417), 741–744 (2003).

58. Melanoma Focus. Melanoma patient decision aid (2019). https://pda.melanomafocus.com/

59. Melanoma Institute Australia. Melanoma Risk Assessment Tool v1.0 (2020). https://www.melanomarisk.org.au/

60. Hyatt A, Drosdowsky A, Williams N *et al.* Exercise behaviors and fatigue in patients receiving immunotherapy for advanced melanoma: a cross-sectional survey via social media. *Integr. Cancer Ther.* 18, 1534735419864431 (2019).

61. Melanoma UK. My Melanoma App. https://www.melanomauk.org.uk/the-patients-voice-digitally

62. Domecq JP, Prutsky G, Elraiyah T *et al.* Patient engagement in research: a systematic review. *BMC Health Serv. Res.* 14, 89 (2014).

63. Cancer Research UK. Cancer statistics for the UK. Cancer Resarch UK, (2020). https://www.cancerresearchuk.org/health-professional/cancer-statistics-for-the-uk

64. Cheese I. Patient perspective: life in the melanoma patient community and the emergence of the melanoma patient conference. *Melanoma Manag.* 4(2), 89–93 (2017).

- **Offers a direct patient perspective on development of a patient- and carer-focused melanoma conference and the role of a patient advocate.**

65. National Institute for Health Research. Public involvement in systematic reviews: Supplement to the briefing notes for researchers (2012). https://www.invo.org.uk/wp-content/uploads/2012/10/INVOLVEPublicInvolvementSystematicReviews2012.pdf