Making Outcome-Based Payment a Reality in the NHS

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NHS in Greater Manchester

CANCER RESEARCH UK

Together we will beat cancer

Office of Health Economics Research

RAND EUROPE

KING'S College LONDON

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Cancer Research UK and Greater Manchester Health and Social Care Partnership commissioned the Office of Health Economics, RAND Europe and Kings College London to carry out the research underpinning this report.

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Cancer Research UK

Cancer Research UK is the world's largest independent cancer charity dedicated to saving lives through research. We support research into all aspects of cancer through the work of over 4,000 scientists, doctors and nurses. In 2017/2018, we spent £423 million on research institutes, hospitals and universities across the UK. We receive no funding from Government for our research.

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Corrigendum

Please note that a sentence on page 126 has been corrected since the original publication. For reference and convenience, the original and corrected sentence follows:

Original

SACT represents a national, inclusive dataset containing data from over 600,000 English patients, which allows patient-level linkage to other PHE-held datasets.

Corrected

SACT represents a national, inclusive dataset containing data from over 600,000 patients treated in England (at time of publication), which allows patient-level linkage to other PHE-held datasets.

List of Acronyms

AAR	Accelerated Access Review
AIFA	Italian Medicines Agency
BCI UK	Bowel Cancer Intelligence Centre UK
BDM RESC	Biomedical and Health Sciences, Dentistry, Medicine and Natural and Mathematical Sciences Research Ethics Subcommittees
CDF	Cancer Drugs Fund
CED	Coverage with Evidence Development
CO	Clinical Outcomes
COSD	Cancer Outcomes and Services Dataset
CPRD	Clinical Practice Research Datalink
CRUK	Cancer Research UK
EAMS	Early Access to Medicines Scheme
EDSS	Expanded Disability Status Scale
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire -C30
EQ-5D	EuroQol Five-Dimensional
ESMO	European Society for Medical Oncology
FDA	(US) Food and Drug Administration
GMHSC	Greater Manchester Health and Social Care Partnership
HES	Hospital Episode Statistics
HRQoL	Health-Related Quality of Life
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MEA	Managed Entry Agreement
MHRA	Medicines and Healthcare products Regulatory Agency
NCRAS	National Cancer Registration and Analysis Service
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OBP	Outcome-Based Payment

OHE	Office of Health Economics
ONS	Office for National Statistics
OPCS	Office of Population Censuses and Surveys
PAS	Patient Access Schemes
PBRSA	Performance-Based Risk-sharing Arrangement
PHE	Public Health England
PPRS	Pharmaceutical Price Regulation Scheme
PRE	Patient-Reported Experience
PREM	Patient-Reported Experience Measure
PRO	Patient-Reported Outcome
PROM	Patient-Reported Outcome Measure
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
REA	Rapid Evidence Assessment
RECIST	Response Evaluation Criteria In Solid Tumors
RTDS	National Radiotherapy Dataset
RWE	Real-World Evidence
SACT	Systemic Anticancer Therapy
SMC	Scottish Medicines Consortium
VAT	Value Added Tax

List of Figures and Tables

Foreword

Cancer Research UK's ambition is for three in four patients to survive their cancer for 10 years or more by 2034. This will require diagnosing more cancers earlier, when treatment is more likely to be successful. But even for cancers diagnosed at the same disease stage, UK cancer patients' survival still lags behind comparable countries internationally. This suggests more could also be done to ensure every patient is receiving the best evidence-based treatment.

Cancer medicines are a crucial part of many patients' treatment and care, and access to these drugs is a hugely emotive issue for people affected by cancer and the wider public. Recent years have seen real improvements in UK patients' access to newly-launched cancer drugs. As this report sets out, exploring more flexible ways to pay for some cancer medicines, such as outcome-based payment (OBP), holds exciting potential to keep improving access to drugs by linking a drug's price to the outcomes it delivers for patients in the NHS.

Both the October 2016 Accelerated Access Review and the August 2017 Life Sciences Industrial Strategy called on Government and the NHS to implement flexible pricing models to support quicker adoption of innovations. And the new Voluntary Scheme for Branded Medicines Pricing and Access – an agreement between the Government and pharmaceutical companies which came into effect at the start of 2019 – committed to increasing commercial flexibilities for companies whose products offer significant value for the NHS.

The increasing number of cancer patients, and the intensity of care they receive, means resources must be spent on interventions that genuinely improve patient outcomes and experience. And our understanding of cancer as a disease is constantly evolving, leading to newer, more personalised treatments such as precision medicines and immunotherapies, but also adding complexity and cost. We know that cancers change over time and can become less responsive to individual medicines, and for many cancer types there are multiple drugs now available at different points in the patient pathway.

We believe OBP provides an important extra option which can be used when the NHS and a company cannot quickly agree a single, fixed price for a new cancer drug, and prolonged negotiations risk delaying or even limiting patient access. There are several trends which will make an OBP approach valuable and, importantly, realistic in the near future:

1. An increasing recognition that evidence of a drug's effectiveness from clinical trials – while essential to prove a drug's safety and efficacy – may not always reflect a medicine's benefits to patients in a routine clinical setting. This may lead to a greater emphasis on using real-world data of patients' treatment outcomes to agree a price that better reflects the drug's true benefit to NHS patients.
2. Many drugs are now being considered for use in the NHS with less mature clinical trials data on their effectiveness than in the past. Innovations should reach patients quickly, but this increases uncertainty about the drug's appropriate price. Complementing clinical trials data with real-world evidence could help maintain quicker patient access while still capturing the drug's long-term benefits, to help judge its value to patients. The data environment in cancer is more advanced than in many other disease areas, making it easier to achieve this.

3. Many of the latest cancer drugs are more complex and expensive than past medicines. This creates greater financial risk to both the NHS and manufacturers from agreeing a price which does not reflect the drug's true value, making negotiations to agree a single fixed price more difficult.

Implementing OBP requires understanding the treatment outcomes that matter most to patients, including factors beyond purely physical health outcomes. This research captures a range of these factors in the outcomes "flower" developed in our research, and which is shown throughout this report. Although what matters to patients will differ across a range of characteristics, people affected by cancer we surveyed identified a common core of priority outcomes to form the basis for an outcome-based programme.

The gain for patients from this new way of paying for cancer drugs is potentially twofold: faster access to innovative drugs where current pricing mechanisms are insufficient; and a greater focus on building NHS structures and services around accurate and explicit measures of the value that they receive from their treatment. Both of these factors should ultimately help to drive improvements in patient outcomes.

In Greater Manchester specifically, cancer incidence rates have historically been above the national average. But the devolution agreement, signed in 2014, provides an opportunity for innovations to be trialled locally, and for the region's health and social care institutions to work together more closely. All of this makes Greater Manchester a fantastic test bed for the kind of emerging, challenging thinking which will be required to design an OBP system for cancer medicines, which could then be feasibly tested in practice.

OBP schemes have existed in the NHS previously, but they have not been used systematically, in part due to a lack of consensus between all the relevant parties. We're pleased to have brought together a range of stakeholders – including government, NHS England, arm's-length bodies, the pharmaceutical industry, and crucially people affected by cancer – to develop a shared vision on this topic for the first time.

This report is the culmination of the first phase of our research in this area. We look forward to continuing to work with our partners to identify and overcome the barriers to implementing OBP within the NHS in England in the next stage of our research.

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Executive Summary

Cancer Drugs Access and Pricing in the UK

More than 360,000 people are diagnosed with cancer in the UK every year, and it's estimated that the UK spends around £2 billion each year on cancer medicines. In England, around 28% of all patients receive cancer drugs as part of their primary treatment, and this proportion is significantly higher for those diagnosed with advanced disease. In order to ensure the best quality care for these patients, it is vital they are able to access the most innovative and effective medicines for their condition.

After their safety and efficacy are proven in clinical trials, all new cancer drugs are reviewed through a process called health technology assessment (HTA), led by the National Institute for Health and Care Excellence (NICE) or the Scottish Medicines Consortium (SMC), to judge if the drug is value for money. If the medicine is not cost effective at the price initially proposed by the manufacturer, they can negotiate a different pricing arrangement. Many negotiations currently conclude with a simple percentage discount on the medicine's price.

Moves to bring new medicines to patients as early as possible are positive. However, this can contribute to uncertainty about the benefits the medicine offers to patients compared to existing treatment options, as the full evidence is still emerging. A drug's benefit may also differ in real-world healthcare practice to what was found in clinical trials. This therefore introduces uncertainty about what the NHS should pay.

Together with the increasing cost and complexity of new medicines, this may make it harder for the NHS and manufacturers to agree a single price for a medicine, potentially resulting in delays in patient access. More flexible ways for the NHS to pay for medicines could, in part, provide a solution.

Figure E1: Rationale for flexible pricing

Cancer Research UK and Greater Manchester Health and Social Care Partnership (GMHSCP) commissioned the Office of Health Economics and RAND Europe, in collaboration with Professor Richard Sullivan of King's College London, to explore the feasibility of introducing one type of flexible payment mechanism – outcome-based payment (OBP) – for cancer medicines into the NHS in England. This model links the price the NHS pays for a medicine to the outcomes it achieves in practice for NHS patients.

OBP could help to accelerate patient access to some new medicines and ensure close monitoring of real-world patient benefit. It can also promote value for money in NHS spending and support innovation emerging from manufacturers. This is especially valuable against the backdrop of rising overall NHS spending on medicines, and of the uncertainty created by the UK's imminent withdrawal from the European Union.

The research focused on establishing the treatment outcomes people affected by cancer consider most important, to inform an OBP approach. It included literature reviews, interviews with stakeholders, focus groups and a survey of cancer patients and carers.

Based on our findings and analysis we make several recommendations for taking forward OBP for cancer medicines both within Greater Manchester (with its devolved responsibility for NHS and social care) and at a national level. We have focused on specific arrangements in the NHS in England, including the national cancer data infrastructure, which represents a key foundation for any OBP scheme. However, our findings and conclusions remain relevant to decision-makers in the other UK nations and health care systems internationally.

Defining Outcome-Based Payment

Outcome-based payment (OBP) schemes are commercial arrangements where a medicine's price is linked to the outcomes achieved for patients receiving the medicine in real-world clinical practice. Medicines that perform as expected and deliver pre-agreed outcomes are reimbursed at the pre-agreed price, while medicines that do not deliver on these outcomes are reimbursed at a lower price or not at all.

This definition encompasses a range of different possible models identified in our literature review, listed in Table E1, which vary in characteristics including how financial risk is shared between the company and the payer (i.e. the NHS in the UK context), and whether the link is dependent on population-level or individual patient outcomes.

Table E1: OBP scheme categories and definitions

Scheme category	Definition
Cost sharing arrangements	Price reduction for initial treatment cycles until it is clear whether a patient is responding to the medicine.
Payment-by-results	Manufacturers reimburse the payer in full in instances where the patient does not respond to the treatment.
Risk sharing	Manufacturers reimburse a proportion of the cost of the medicine for non-responders.
Outcomes guarantees / pay-for-performance	Manufacturer provides rebates, refunds or price adjustments if the medicine fails to meet pre-agreed outcome targets at the individual patient level.
Coverage with evidence development	Access to a drug is initially provided on the condition that further population-level evidence is gathered. Based on this further evidence the payer then makes a decision whether to continue funding the treatment or not.
Conditional treatment continuation	Payment for the continued use of a given drug is based on intermediate endpoints at the individual patient level.

OBP schemes are already in use in the UK, for cancer and non-cancer medicines. For example, in November 2017, NHS England announced it had agreed "pay by cure" deals for medicines to treat Hepatitis C and Multiple Sclerosis, which it badged as the latest in "a series of outcome-based payment arrangements". There are also numerous examples of OBP schemes being used globally in countries including Australia, Italy and the Netherlands. These examples suggest that wider implementation of OBP for cancer medicines in the NHS is possible.

It is worth noting the reformed Cancer Drugs Fund (CDF), allowing NICE to conditionally approve cancer medicines and collect real-world evidence of their benefits (for use alongside clinical trials data in a later HTA reassessment), is effectively a type of OBP scheme, a form of "coverage with evidence development". Over 7,500 patients received "managed access" drugs in this way between July 2016 and September 2018, demonstrating the value of this flexibility.

Scope of Outcome-Based Payment Use

Our research also identified challenges to successfully designing and implementing OBP schemes. These included the timeliness and quality of the real-world data collected; concerns around administrative complexity; and ensuring there is consensus from both payers and manufacturers on the outcomes which will be used to determine price.

However, there was consensus among stakeholders we interviewed that these challenges could be overcome if all parties have the will to do so, and there is a clear benefit to patients, the NHS and industry. This suggests that while OBP may be unnecessarily complex for many medicines, it can play a role in facilitating patient access where a simple fixed price cannot be negotiated in good time – for example where there is uncertainty about a drug's effectiveness based on clinical trials data, but the drug is felt to offer a reasonable prospect of significant clinical benefit in practice in the NHS.

Figure E2: Characteristics of medicines suitable for OBP

In the interests of transparency, and to help ensure and monitor good practice in the design of OBP schemes, a basic level of information about any schemes agreed between the NHS and manufacturers should be made public. This does not need to include commercially sensitive information but should indicate which outcomes are measured, the source of the data for the outcome metrics being used and how those outcomes are linked to price. This would help avoid unnecessary duplication of effort in the design of OBP schemes and inform conversations about the scale of the challenges in implementing OBP in the NHS.

Recommendation: *GMHSCP, Government, NHS England, the pharmaceutical industry, NICE and all other relevant stakeholders should continue to explore the use of OBP schemes, with the aim of facilitating patient access to cancer medicines in cases where a simple discount on the medicine's list price cannot be agreed on a timely basis. Conversations should be taken forward on a joint basis, through forums and initiatives such as the Accelerated Access Collaborative.*

Recommendation: *GMHSCP, Cancer Research UK, NHS England, NICE and the pharmaceutical industry should work together to horizon scan medicines nearing regulatory submission which might be suitable for an OBP scheme. We believe such medicines would have the following characteristics:*

- *Potentially large benefit to patients receiving the medicine*
- *Small to moderately-sized patient populations*
- *Immature clinical trials data*
- *A disease profile where improvements in outcomes measurable in the short-term (including overall survival and non-progression/relapse) are particularly valuable.*

Recommendation: *NHS England or NICE should publish information on how outcomes are measured and linked to price in any OBP schemes for medicines in operation in the NHS. This should stop short of publishing commercially sensitive financial information.*

Which Outcomes Should Be Measured?

The use of OBP schemes could formalise the use of a broader range of outcomes than is currently systematically captured in the HTA process. It would also allow a medicine's price to be varied in the light of real-world evidence of its effectiveness in routine NHS use. Taken together, these factors could mean this price more closely aligns with the true value of that medicine to patients in an NHS setting (beyond clinical trials). Our research established the full scope of outcomes to be considered, as set out in Figure E3 below.

Through further engagement with patients and carers, a set of four outcomes (survival; disease progression, relapse or recurrence; long-term side effects; and return to normal activities) was identified as of greatest importance. We therefore recommend these four outcomes should form the "core" of any future OBP schemes negotiated by NHS England and pharmaceutical companies for cancer medicines, as set out in Figure E4 below.

NICE's HTA processes refer to all of these types of outcomes when deciding whether a new medicine should be reimbursed by the NHS, and the four outcomes listed will all affect whether NICE judges a medicine to be cost-effective. However, data on some of these outcomes would not currently be routinely captured in NHS clinical practice, particularly "long-term side effects" and "return to normal activities".

Our research has highlighted the importance of formally and explicitly using these outcomes when designing an OBP scheme for cancer medicines. Recognising these outcomes in future OBP schemes would ensure that real-world evidence of a drug's impact on these outcomes could be collected and used to align its price with the value it delivers to patients in the NHS, based on the outcomes that matter most to patients.

Figure E3: Outcomes "flower"

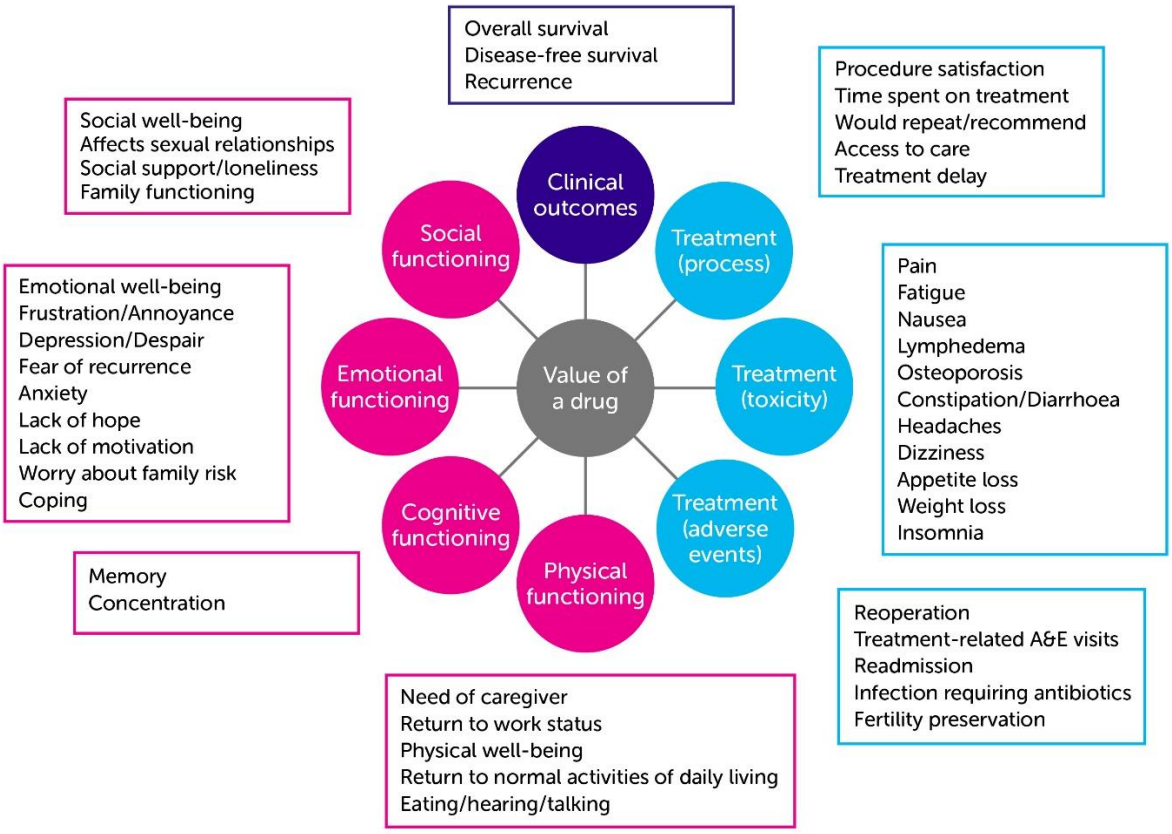
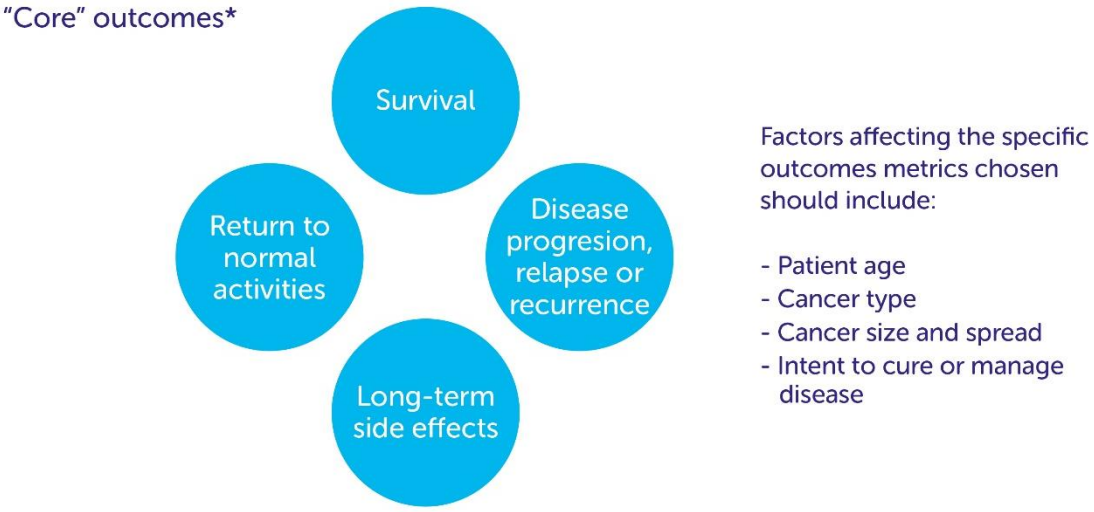


Figure E4: Outcomes framework



*The treatment outcomes identified as the most important to people affected by cancer in our survey. We recommend the price the NHS pays for a drug under any future OBP scheme should be linked to NHS patient outcomes in these four areas.

Given a chosen set of outcome measures for a specific OBP scheme, there remains a need to understand the relative weights to be attached to those measures, and how the resulting composite measure of outcomes is linked to the price paid for the medicine. Options for achieving this should be explored in future research.

Recommendation: *As part of any future OBP schemes negotiated between NHS purchasers of cancer medicines and manufacturers, specific metrics should be included to measure the drug's effects on patients in the NHS, on the following four types of outcomes as standard:*

- *Survival*
- *Disease progression, relapse or recurrence*
- *Long-term side effects*
- *Return to normal activities*

Recommendation: *Future research into the use of OBP in the NHS should investigate the relative weights which should be attached to measures of the four "standard" outcomes (and potentially others) we wish to see included in future OBP schemes. This should include seeking the views of patients and other key stakeholders. This research should also clarify options for linking outcomes to a drug's price in practice.*

Real-World Data Infrastructure

Real-world outcomes can be linked to price in a number of different ways, though our research has found that "binary" or "stepped" options (with a limited number of possible price points) are preferable to "continuous" schemes in order to minimise complexity. However, high-quality data on a drug's real-world benefits is needed to establish this link in the first place – although OBP schemes can also include the collection of additional trial data as well.

The cancer data infrastructure in England is already able to capture some of the "core" outcomes outlined above, including patient survival. However, these data are not always high-quality or complete. There also remains a need to explore to what extent data on other outcomes of importance (including long-term side effects and return to normal activities) are collected, where they are captured if so, and whether it is possible to link these with data on other outcomes in the way that would be required to operate an OBP scheme.

Determining how each outcome is measured for any given OBP scheme will need to consider the practicalities of data collection in the NHS with the current data infrastructure, and the need to avoid excessive administrative burden. A strong message from stakeholders interviewed is that, to succeed, OBP schemes need to be simple to operate.

Recommendation: *Future research into the use of OBP in the NHS should investigate with NHS staff the practicalities of collecting data for an OBP scheme, based on exemplar medicines and for measures of the four outcome types listed earlier.*

Recommendation: *As part of future research into the use of OBP in the NHS, a mapping exercise should be undertaken to ascertain the appropriate data sources, and identify "gaps" in the capacity to collect data on the "standard" outcomes specified above. This review should involve NHS Trusts providing cancer care, Public Health England, NHS England and the pharmaceutical industry.*

Recommendation: *NHS England and Public Health England should ensure resource is available within PHE to monitor and analyse in a timely manner the data submitted to SACT as part of any future OBP schemes adopted in the NHS nationally; and should explore the feasibility of using SACT or another consolidated database to capture all four "standard" outcomes, in order to facilitate their inclusion in future OBP schemes.*

Contents

1 Introduction

1.1 Translating medical advances into patient access

More than 360,000 people in the United Kingdom (UK) are diagnosed with cancer each year.[1] Of these, around 28% receive cancer drugs as part of their primary treatment (estimates from England), though this proportion is significantly higher for those diagnosed when their disease is more advanced.[2] In order to ensure the best quality care for these patients, it is vital they are able to access the most innovative and effective medicines for their condition.

It is estimated the UK spends around £2 billion each year on cancer medicines,[3] and growth in oncology medicines spending globally is expected to increase on average by 10-13% over the next five years.[4] Much of the recent and anticipated future growth in spending can be attributed to advances in the development of cancer medicines: in 2005 there were 399 cancer drugs in development in the US (in clinical trials or awaiting review by the Food and Drug Administration (FDA)), while today there are an estimated 1,120.[5] Many of these new medicines are more effective, but also significantly more expensive, than medicines used in the past.

Translating this scientific progress into routine access to innovations for cancer patients remains a challenge globally. Of the 55 oncology drugs launched between 2012 and 2016 only patients in the US, Germany and the UK have access to more than 40 of these medicines.

1.2 Challenges to patient access

Whether a medicine is efficacious and safe, and hence can be licensed for use in the UK, is determined by one of two bodies: the European Medicines Agency (EMA) on a Europe-wide basis, or the Medicines and Healthcare products Regulatory Agency (MHRA) for the UK alone.

Many new treatments are being approved by regulatory agencies (including the EMA) with increasingly immature or incomplete data. Approval based on immature or incomplete data can be a particular issue in cases where the patient group is small, or where outcomes only become clear in the long-term, beyond the timescale of a clinical trial. The result is then uncertainty about the extent of a medicine's effectiveness.

This poses a challenge to patient access, since in many countries there is an additional step before a licenced cancer drug (one that has regulatory approval) can be made available to patients (either reimbursed publicly or via an insurance scheme). Its comparative clinical effectiveness and – in many tax-funded health care systems, including the UK – its cost effectiveness must be evaluated, via a process called health technology assessment (HTA).

In the UK, before a patient has access to a cancer medicine on the National Health Service (NHS), the drug's clinical and cost effectiveness must be assessed by the National Institute for Health and Care Excellence (NICE) in England (whose decisions are usually also applied in Wales and Northern Ireland), and by the Scottish Medicines Consortium (SMC) in Scotland.[i] This step helps to ensure that the NHS is spending its limited resources on interventions which offer the greatest benefit for their cost.

[i] Note that the Early Access to Medicines Scheme is an exception to this, see the following Chapter for details.

The clinical and cost effectiveness of new drugs is normally evaluated by NICE and the SMC with data from clinical trials. Such trials are vital for establishing the safety and efficacy of treatments (thereby informing regulatory approval). Clinical trials data are also used to inform any price negotiations between the drug manufacturer and the NHS.

While the evidence of a drug's clinical benefit from trials is crucial for establishing safety and efficacy, trial evidence often fails to reflect the outcomes that will be achieved when used in a real-world setting, as the trial patients and setting often don't reflect routine clinical practice or the mix of patients who are treated. For example, in real-world practice some patients will have comorbidities along with their cancer, but patients in the clinical trials will have been selected to be without such comorbidities.[6] This creates further uncertainty about the cost effectiveness of the new medicines. Together with the uncertainty arising from immaturities or gaps in the clinical trial data, this may lead to delay in patients being given access to them.

1.3 Overcoming the challenge

In light of these challenges, and in the context of the continuing financial pressures on the NHS, it is increasingly important that alternative approaches to improving access are explored. A number of policies have been implemented in the UK to help ensure an appropriate balance between speed of patient access to new medicines and evidence of their effectiveness, including in England reforms to the Cancer Drugs Fund (CDF).

The Accelerated Access Review (AAR) made a number of recommendations to government in 2016 to improve patient access to new technologies,[7] many of which were then also advocated by the 2017 Life Sciences Industrial Strategy (LSIS).[8] Specifically, the LSIS supported the proposal from the AAR that NHS England should adopt more flexible pricing mechanisms to assist the reimbursement of products (including medicines) under early access schemes.

Flexible pricing schemes, supported with real-world evidence of the benefits of these technologies, offer a potentially effective response to the challenges of access to medicines outlined above. They give the NHS the option of the price it pays for a medicine being adjusted in the light of experience, removing some of the risk of overpaying for products which do not deliver the expected benefits in practice.

Flexible pricing schemes already exist to some degree in the NHS. We wish to build on existing practice and understand whether flexible pricing is appropriate for, and could improve patient access to, at least some of the cancer drugs currently in development or seeking regulatory approval, and what principles should underlie such arrangements if so.

1.4 Aims and scope

Cancer Research UK and Greater Manchester Health and Social Care Partnership (GMHSCP) wish to explore the possibility of developing a new model of paying for some cancer drugs within the NHS, both in Greater Manchester and more widely, explicitly on the basis of the outcomes they achieve. Such an approach is called outcome-based payment (OBP), and is an example of flexible pricing. It is described in detail in Section 3, but in summary OBP aligns a medicine's cost to the NHS (and the reimbursement to its manufacturer) with the benefits it delivers for patients in the real world.

As the first phase of this work, this study has been undertaken to:

1. Produce a body of evidence that can underpin criteria to evaluate the real-world benefit of a new cancer drug, taking particular account of the views of patients.
2. Define these criteria, which will provide a benchmark for future OBP schemes for cancer drugs with cancer-specific measures.
3. Produce pragmatic evidence that is transferable to a clinical setting in the NHS in England, and can be used to improve patient outcomes and drive value for the health service – taking into consideration the existing capabilities in NHS and UK datasets, as well as the potential for future indicators to be developed.

To meet these objectives, the team first reviewed the published literature on OBP schemes for medicines in use around the world, and the range of outcome measures for cancer medicines. Given that information, stakeholders (13 in all) including clinicians, industry, NHS commissioners of cancer services and international academic experts were then interviewed for their insights.

To obtain the views of patients and carers on the treatment outcomes they prioritised, two focus groups and then a survey were conducted. In parallel a brief review of data collected by the NHS on cancer outcomes was also undertaken. Box 1 describes the overall methodology more fully and the Appendices set out the details of each element of the research.

Although this report's recommendations are focused on England only, the research findings presented in this report have potential applicability internationally as well as in all four nations of the UK. The international review of research and practice on OBP and the development of an outcomes framework, are steps towards implementing OBP and improving patients' access to new cancer medicines.

Box 1 – Methodology

The findings in this report are based on both **qualitative and quantitative analysis**, using a combination of literature reviews, interviews with key stakeholders and experts in the field, and engagement with patients through focus groups and a patient-focused survey. Ethical approval for the primary data collection with stakeholders and patients was provided by King's College London.

Literature reviews were undertaken to systematically identify two sets of literature:

- Existing studies of, and descriptions of, schemes to link the outcomes achieved by use of new medicines with the price or reimbursement of that medicine paid by health care payers. Note this was not restricted to just schemes for cancer drugs. Appendix 1 provides further details of the methods and accompanying results.
- Cancer treatment outcome measures, including clinical outcomes, patient reported outcomes and patient experience measures that might be practical to collect in the context of the NHS in England (see Appendix 2).

The information extracted from the two literature reviews provided information for the design of 13 semi-structured **qualitative interviews** with clinicians; commissioners of cancer services; and pharmaceutical industry and academic experts in the field of OBP schemes. These interviews allowed us to test the implications of the findings from the literature review with a range of relevant stakeholder groups – with the exception of patients and their carers, whose views we sought instead via focus groups and a survey.

The interviews probed the practicality of options for measuring cancer medicines' outcomes and collecting the corresponding data (or repurposing existing data collections); and on how to link the measured outcomes to the price paid by the NHS for the medicines used. See Appendix 3 for further details of the methods and accompanying themes identified in the analysis of the interviews.

Focus groups with patients were held to gain an understanding of their views on treatment outcomes and their views on patient experience. The first focus group (with five cancer patients) evaluated the comprehensiveness of an outcomes framework derived from the literature review. A second focus group (with four cancer patients) used a method of card sorting to collapse the outcomes into more defined categories and identify a hierarchy of importance, producing a refined short list that was then included in a survey. See Appendix 4 for further details of the methods and accompanying results of the focus groups.

A **survey** which was targeted at both cancer patients and carers elicited rankings of ten types of outcomes from the use of cancer medicines. The online survey was completed by 164 respondents and the importance of each outcome was analysed according to the respondent's cancer experience and personal characteristics (see Appendix 5).

Finally, a brief review of the **data held by the NHS** on cancer outcomes was undertaken (see Appendix 6).

Taking into account all of the evidence collected, we then make eight recommendations for actions to enable OBP to be realised within the NHS, both in Greater Manchester and England more widely.

The project was overseen by a **Steering Group** including individuals from Cancer Research UK, GMHSCP, NHS England, the Department of Health and Social Care (DHSC), the National Institute of Health and Care Excellence (NICE), Public Health England (PHE), the pharmaceutical industry and patient representatives. Individuals' participation in the Steering Group was as subject experts rather than representatives of their respective organisations. See Appendix 7 for acknowledgements.

2 Current Funding Landscape

2.1 Drug Approval and the Role of Patient Outcomes in Reimbursement Decisions

The European Medicines Agency (EMA) is responsible for providing regulatory approval of new drugs (and new indications for existing drugs) in the European Union.[ii] The EMA evaluates safety, quality and efficacy (that is, whether a drug works). Once a drug is licensed, a doctor in the UK can legally prescribe it, but wider availability on the NHS is only possible with approval from an HTA organisation (NICE and the SMC). NICE and the SMC evaluate whether it is better than current alternative treatments (comparative effectiveness) and if it offers value for money (cost effectiveness).[9]

When assessing effectiveness, in other words patient outcomes, the NICE reference case recommends the use of quality-adjusted life-years (QALYs), which combine length of life with health-related quality of life measured using the EQ-5D instrument. The EQ-5D is made up of both descriptive elements of health (e.g. pain, mobility, self-care), and an overall evaluation by the patient of self-rated health status using a visual analogue scale from 0-100 (with higher ratings representing better health status). QALYs can be compared across a range of health conditions and diseases, aiding the comparability of conditions and treatments which have either morbidity or mortality effects (or both).

NICE decides if a drug is both clinically and cost effective and thus beneficial to introduce into the NHS. Cost effectiveness is often compared to a cost effectiveness threshold, which NICE defines as £20,000-30,000 per QALY gained (or a higher amount for end of life medicines, up to £50,000 per QALY gained). But QALYs are not the only basis for decisions. There are examples of NICE considering additional outcomes based on the implementation of social value judgements as part of the decision criteria – see Box 2 below.

NICE's Citizens Council has listed circumstances that could support the use of an alternative (higher) cost effectiveness threshold:[10]

- the patients are children;
- the illness is rare, extremely severe and could be a result of NHS negligence;
- the treatment is life-saving, prevents harm in the future, has a major impact on the patients' family, and encourages scientific and technical innovation.

Box 2 – Case study of NICE's social value judgement

In August 2018, NICE published guidance recommending dinutuximab beta as an option for treating high-risk neuroblastoma, a rare type of cancer, primarily affecting children. The appraisal committee took into consideration "the uncaptured health-related benefits, the rarity and severity of the disease and the potential lifetime benefit for children with neuroblastoma". The committee also noted the impact that the disease can have on carers and family members, which indirectly points towards outcomes such as anxiety, stress and disruption to working life.[11]

[ii] At the time of writing the role of the EMA in the UK once the UK has left the EU is unknown. The Medicines and Healthcare products Regulatory Agency (MHRA) can undertake a similar role but solely for the UK.

2.2 Pricing Arrangements

Once NICE makes a positive recommendation through its technology appraisal programme that a drug should be available for NHS use, the NHS in England is mandated to fund and resource it if the doctor responsible for the patient's care deems it clinically appropriate.

The NHS generally pays a fixed single price set in advance of the medicine being purchased, via negotiation with the drug's manufacturer. However, it is possible under the current NICE processes for manufacturers to propose flexible pricing arrangements including outcome-based patient access schemes and commercial access agreements (set out in Section 4 in the Guide to process of technology appraisal). Basic details of these are published, but much of the information is likely to be commercially confidential.

The price negotiated is most often based on clinical trial evidence about the effectiveness of the medicine. However, it is widely acknowledged that the experience within a trial and the outcomes achieved in a trial setting do not necessarily align with real-world outcomes. By design randomised controlled trials (RCTs) are limited to a subset of patients who are not fully representative of the real-world population. RCTs tend to exclude patients who are very young, very old or who have major comorbidities (other illnesses experienced at the same time as the one being treated by the medicine in question), whilst trial participants show higher treatment adherence than those in clinical practice.[12]

Given the potential for misalignment between trial outcomes and real-world outcomes, there is a financial risk, for both the payer and the manufacturer, if the price is set incorrectly. As noted in the Introduction, the current environment is one of innovative but expensive new drugs, accompanied by a growing impetus for accelerated regulatory approval and early patient access to drugs with less mature trial evidence; thus the risk is increasingly relevant.

2.3 Current Access and Pricing Initiatives

In England, the need to strike an appropriate balance between accelerated regulatory approval, and ensuring that approval is based on clear evidence of a medicine's effectiveness, has resulted in initiatives such as the Early Access to Medicines Scheme (EAMS) and the Cancer Drugs Fund (CDF).

EAMS, which was launched in April 2014, aims to give patients access to drugs that do not yet have regulatory approval but where there is a clear unmet medical need due to the condition being life-threatening or seriously debilitating. The timelines for EAMS are such that products with a positive EAMS opinion could be available to NHS patients some months before marketing authorisation is granted. The expectation is that products will be provided to the NHS free of charge during the EAMS period.

The EAMS period also offers a chance for real-world data on the drug's effectiveness to be collected, which can be used to complement existing clinical trials evidence in the subsequent HTA process. As set out in the EAMS operational guidance, should the MHRA grant a promising innovative medicine (PIM) designation, NHS England and NICE may then work with the manufacturer to discuss data collection plans through the EAMS period.

In 2011 the Government established the Cancer Drugs Fund (CDF) to allow cancer patients in England to access drugs not routinely available on the NHS. This function was retained when the CDF was reformed in 2016 to create a managed access fund providing temporary access to promising medicines.

This reform set clear criteria on which cancer medicines the CDF will fund and for how long. Rather than rejecting those cancer drugs for which the HTA process has identified significant uncertainty around their long-term clinical and cost effectiveness, NICE can offer conditional approval – recommendation for use within the CDF – which usually involves collection of real-world data to help resolve that uncertainty. After an agreed time period, NICE then evaluate the drug again, using updated clinical trials data and real-world evidence depending on availability of each.

Between July 2016 and September 2018, over 7,500 patients accessed conditionally-approved "managed access" drugs through the CDF,[13] and that number is set to rapidly increase as more drugs are approved for use in the Fund.

We see flexible medicines pricing, including outcome-based payment (OBP), as a logical next step which can make use of knowledge gained from the experience of these and other initiatives. The CDF in particular provides a strong foundation for the wider use of OBP for cancer medicines within the NHS in England, since conditional approval with the collection of real-world evidence (as in the reformed CDF model) is a type of OBP scheme (specifically referred to as coverage with evidence development – see the following Chapter for details).

The October 2016 Accelerated Access Review (AAR) also endorsed the use of flexible pricing in this context. It suggested that for the NHS to routinely promote early access requires significant commercial dialogue between policymakers and industry, so that mutually advantageous arrangements can be agreed quickly.[7] In particular, the Review suggested this dialogue could include consideration of novel risk-sharing agreements such as flexible pricing, which recognise uncertainty in the evidence base and where the benefits of accelerated access can be shared across stakeholders.

3 What is Outcome-Based Payment?

3.1 Why Outcome-Based Payment?

As outlined in the previous Chapter, there is growing interest in flexible forms of pricing for cases when the effectiveness of a medicine in real-world practice remains uncertain despite clinical trials. One way to overcome the problem of uncertainty about a medicine's effectiveness, without simply extending the duration of clinical trials and hence delaying further the general availability of the medicine, is outcome-based payment (OBP).

OBP is where the price paid for the medicine is linked to the real-world outcome(s) it actually achieves for patients. If the medicine works as expected based on the clinical trials then a predetermined price is paid, but if the medicine works less well a lower or zero price applies. It could in principle also be the case that should a medicine work better than expected then a higher price is applied.

OBP can serve to give a clear signal to pharmaceutical companies that they will be paid for the value their new medicines deliver in a real-world setting relative to the existing standard of care; and simultaneously ensure that the NHS is only having to pay for a medicine to the extent that it benefits patients.

3.2 Precedents

Early work on OBP in the UK was linked to a Government proposal for price regulation for new branded medicines that became known as 'value-based pricing' (VBP). The stated aim was to link the price of new medicines of all kinds, not just cancer medicines, to the 'value' they bring. The meaning of 'value' was intended to potentially extend beyond clinical effectiveness.

Sussex et al.[14] set out to identify and describe the range of alternative means by which 'value' might be measured in a VBP approach in the UK. They subsequently described the options available for aggregating the different components of value to establish a maximum price. They concluded that VBP is not without its challenges, particularly around the need for value judgements, and that stages of the VBP process are subject to uncertainty. Consequently, the assessment of overall value can provide bounds to a price negotiation, but it cannot be expected to identify a precise value-based price.

However, during the period VBP was being developed, the Pharmaceutical Price Regulation Scheme for branded medicines was being negotiated which put a cap on total NHS medicines expenditure for the first time, and the impetus behind VBP evaporated before the scheme was designed. Notably there was also considerable opposition to VBP from the industry.

A small number of individual OBP schemes have so far been implemented in the UK. The two clearest examples are described in Box 3 below.

Box 3 – Examples of OBP schemes in the NHS

Velcade (bortezomib) is a medicine for treating relapsed multiple myeloma. Under the OBP scheme in the UK the NHS will pay the manufacturer's price for the medicine for patients at first relapse who achieve a response to Velcade, but for patients who do not respond the pharmaceutical company will provide replacement stock or credit to the NHS. In effect therefore, the NHS does not have to pay for the medicine when it does not work. 'Response' in this case is determined by a clinical measure: to be deemed to have 'responded', the patient must experience a 25% or greater reduction in serum M-protein levels.

Another example of an OBP scheme in the NHS is that for the hepatitis C treatment Olysio (simeprevir). In 2015 Olysio was reimbursed by NHS England under a scheme whereby if the hepatitis virus has not cleared in 12 weeks Janssen (the manufacturer) were to fund the cost of the treatment, so-called "pay if you clear". The procurement approach for Hep C was made possible by NHS England collecting information on medicines being prescribed and patient outcomes measures realised. Notably in this example viral load is a relatively easy clinical outcome to assess.

It is also worth remembering, as context for the discussion of OBP for cancer medicines, that reimbursement of pharmaceuticals is only one element of the health economy and that a variety of payment-for-performance approaches are applied to reimburse and incentivise health services and health professionals in the NHS and elsewhere. Within the NHS there is an 'outcome-based commissioning' movement.[15] The evidence base for the success of this type of commissioning is mixed,[16] although this has not stopped them being more broadly adopted (for example in the Commissioning for Quality and Innovation (CQUIN) Framework in the NHS in England).[17]

3.3 Different forms of OBP

There are many variants of OBP and an even larger number of terms used to refer to them. Table 1 below lists the main categories.[iii] We are interested specifically in where the price paid for a medicine depends in some way on measurement of outcomes.

[iii] For the interested reader, other taxonomies of which kinds of pricing arrangements fit under which titles are provided in other studies.[18] [19]

Table 1: OBP schemes categories and definitions

Scheme category	Definition
Cost sharing arrangements	Price reduction for initial treatment cycles until it is clear whether a patient is responding to the medicine.
Payment-by-results	Manufacturers reimburse the payer in full in instances where the patient does not respond to the treatment.
Risk-sharing	Manufacturers reimburse a proportion of the cost of the medicine for non-responders.
Outcomes guarantees/pay-for-performance	Manufacturer provides rebates, refunds or price adjustments if the medicine fails to meet pre-agreed outcome targets at the individual patient level.
Coverage with evidence development	Access to a drug is initially provided on the condition that further population level evidence is gathered. Based on this further evidence the payer then makes a decision whether to continue funding the treatment or not. The Cancer Drugs Fund arrangements in England are a form of coverage with evidence development.
Conditional treatment continuation	Payment for the continued use of a given drug is based on intermediate endpoints at the individual patient level.

3.4 Implementing OBP

The implementation of OBP will require key steps to be undertaken in agreement between the NHS purchaser of the medicine and the pharmaceutical company selling it, including:[14]

- Identifying the potential outcomes from using the medicine that are to be linked to payment. The outcomes need to be important to patients and clinicians and need to be clearly affected by the medicine, rather than by other or exogenous factors;
- Measuring those outcomes. This requires a metric for each outcome for which data can be collected, but also agreement as to when to measure those outcomes. For example, how long after the commencement or completion of treatment with a medicine should quality of life (or any other outcome) be measured?
- Assigning relative values to the measured outcomes and aggregating them into a composite outcome measure;
- Determining how to link the price to the measured outcome.

This report is concerned with the first two steps: identifying and measuring the outcomes appropriate to new cancer medicines.

Any type of OBP scheme can be used in combination with any particular measured outcome or composite combination of outcomes. NICE and the CDF in England usually measure cancer medicines' outcomes in the form of QALYs calculated on the basis of a particular set of weightings of various quality of life dimensions and years of life.

However, it would in principle be quite possible for a commissioner to use a different composite measure of outcomes, with different constituent elements and/or different relative weights for the elements.

None of the steps is straightforward. As a consequence, while there are OBP schemes in use in several countries' health care systems, the literature review (Appendix 1) shows that in all countries they represent only a small minority of all the medicines in use. Where pharmaceutical companies and health care payers can agree a simple fixed price, or a fixed price plus quantity-related discount, this is still the predominant model. But where significant uncertainty surrounds how well a medicine will work in practice but the potential benefits to patients make it desirable not to wait while further clinical trials are undertaken, then OBP has a role.

The literature review identified many examples of OBP schemes internationally, although no attempt to implement OBP schemes across more than a subset of new medicines. The review revealed the existence of 86 schemes across a range of countries, summarised as follows:

- 26 in the Netherlands,[20]
- 25 in Italy,[20-24]
- 17 in Australia;[25 26]
- Six in the US,[20 21 27 28]
- Four in France,[20 23]
- Four in the UK,[20 21 23 27 29]
- Three in Sweden,[23 30 31] and
- One in Spain.[32]

The greatest numbers of OBP schemes were identified in Australia, Italy and the Netherlands. Rather fewer OBP schemes have so far been implemented in the UK, with the Velcade scheme being the most prominent example here to date – see Box 3 above. It is also worth noting that as many as 75 of the schemes involved measuring clinical outcomes (as opposed to patient reported outcomes, for example) to determine disease progression, making such outcomes by far the most popular in OBP schemes globally.

Different types of OBP can be thought of as varying in the following dimensions, in addition to the particular outcomes and their measures that are used in each case:

- Whether the price is determined for individual patients in turn, as in the Velcade scheme, or whether the price for all purchases of the medicine is adjusted according to outcomes achieved by the whole population of patients being treated;
- Whether the price is initially set high but will be reduced if outcomes do not meet expectations; or is initially set low but will be increased when the medicine has demonstrated that it work; or is initially set at an intermediate level and might subsequently be increased or reduced or left unchanged depending on the outcomes achieved.
- Whether price is linked to outcomes in a binary manner (e.g. one price if the patients respond, another price if they do not); or in a stepped manner (e.g. three or more prices according to whether different levels of outcomes are achieved); or even whether price is a continuous function of the outcome measured.

All of these variants exist in one or more of the schemes that were reported in the literature (Appendix 1). Many of the individual schemes identified through the literature review and/or referred to by some of our stakeholder interviewees (see details of the interview findings in Appendix 3) functioned on the basis of whether individual patients respond, and the price was in effect binary. A price was paid to the manufacturer for patients who responded to the medicine, but the price was wholly or partially refunded for the patients who did not respond.

Other schemes implied that the price for all purchases would be reviewed and might be adjusted downwards based on the average aggregate outcomes achieved across a large number of patients treated. But we did not find reference to price being a direct function of the magnitude of the outcomes achieved. Nor did the literature review reveal any schemes yet in operation where the price of the medicine might be increased if outcomes were found to exceed expected levels, although the CDF does allow for this.

4 Research Findings and Discussion

4.1 Outcomes Framework

Lack of consensus beyond clinical measures

Outcomes in cancer care, and specifically outcomes of cancer medicines are numerous, not always well-defined and there is no general consensus regarding the measurement of outcomes beyond the clinical realm. Garrison and Towse[18] in a discussion of the various 'value frameworks' which have been proposed in the US for new medicines in oncology and other clinical areas, present a broad range of elements of the value of medicines that include gains in life expectancy and improvements in quality of life, but go further to include:

- the value of hope, and willingness to accept greater risk given a chance for a cure
- cost savings outside the health sector
- benefits to subsequent scientific knowledge and progress.

However, our literature review of OBP schemes (see Appendix 1) found that in practice clinical outcomes are most commonly used to determine disease progression and therefore effectiveness in OBP schemes rather than patient reported outcomes. Indeed, our literature review on outcomes (see Appendix 2 for details) failed to identify either a robust core set of outcomes for cancer, or a standardised patient reported outcome measure (PROM) or a patient reported experience measure (PREM) that are commonly used.[iv]

The interviewees we spoke to expected the choice of outcomes to vary according to the specific cancer medicine, the cancer being treated, its site and stage. The importance of quality of life outcomes was widely supported, in addition to survival. There was a desire for outcome measures to be objective, implying that schemes will need to rely on well-validated measures when patient-reported outcomes are included (see Appendix 3).

Difficulties identifying a core set

To illustrate the difficulties found for the identification of a robust core set of outcomes for all cancers, some of the sets of core outcomes suggested in the papers reviewed are described in Table 2 below. A comprehensive version of Table 2 can be seen at Table 7 in Appendix 2.

Note that the concept of 'outcomes' has also been labelled in some of the studies as 'symptoms' or 'domains'. Even for papers using the same term (such as 'domains'),[34 35] the selected items are pointing at different levels of detail (such as 'urinary incontinence' versus 'global quality of life').

The papers which collected cross-cancer outcomes[36 37] focus on symptoms, and exclude other relevant outcomes (such as survival). In addition, there is variability in core outcomes by cancer site. Note also that even papers that address a similar cancer report different core outcomes (as those for prostate cancer).[34 38]

[iv] Note that NHS England is currently developing a new standardised quality of life metric for recovering cancer patient, where they are using questionnaires to measure how effective the care and support of individuals is once treatment ends.[33]

Table 2: Examples of core outcome sets

Reference	Concept	Cancer	Items
Reeve et al., [36] Basch et al.[37]	Symptoms	All	fatigue, insomnia, pain, anorexia, shortness of breath (dyspnea), cognitive problems (includes memory or concentration impairment), anxiety (includes worry), nausea, depression, sensory neuropathy, constipation, diarrhea
Chen et al.[34]	Domains	Prostate	For localised cancer: urinary incontinence, urinary obstruction and irritation, bowel-related symptoms, sexual dysfunction, hormonal symptoms. For advanced cancer: pain, fatigue, mental well-being, and physical well-being
MacLennan et al.[38]	Outcomes	Prostate	survival (death from prostate cancer, death from any cause, local disease recurrence, distant disease recurrence/metastases, disease progression, need for salvage therapy); bowel function (bowel function, faecal incontinence); urinary function (stress incontinence, urinary function); sexual function; quality of life
Macefield et al.[35]	Domains	Oesophageal	**Generic**: emotional function, role physical/activities of daily life, physical function, social function, generic health, sleep, global quality of life, cognition, role emotional, financial issues, spiritual issues

The methodology used in the papers suggesting core outcome sets involved qualitative analysis and subjective assessment, and their findings have a lack of generalisability. Finally, only few of the revised papers discuss the relative importance of measures, and no paper quantifies these relative weights.

Outcomes 'flower'

In order to address the first step in implementing OBP as put forward by Sussex et al.[14] (identifying the potential outcomes that are important and are clearly affected by the medicine) we sought to categorise the various outcomes reported in the papers identified in the literature review into an outcomes framework.

In line with the current literature on outcome value frameworks, which use the visual representation of a 'value flower', an 'outcomes flower' was created, where the centre (the 'pistil') is the value of a drug and the high-level outcomes are 'petals' (see Figure 1). Sitting beyond the petals are the lower-level specific outcomes that were identified in the literature review (see Appendix 2). The explanation of the high-level outcomes (petals) is presented in Table 3. Note that for simplicity the outcomes framework can be presented just with the high-level outcomes as shown in Figure 2.

Figure 1: Outcomes flower

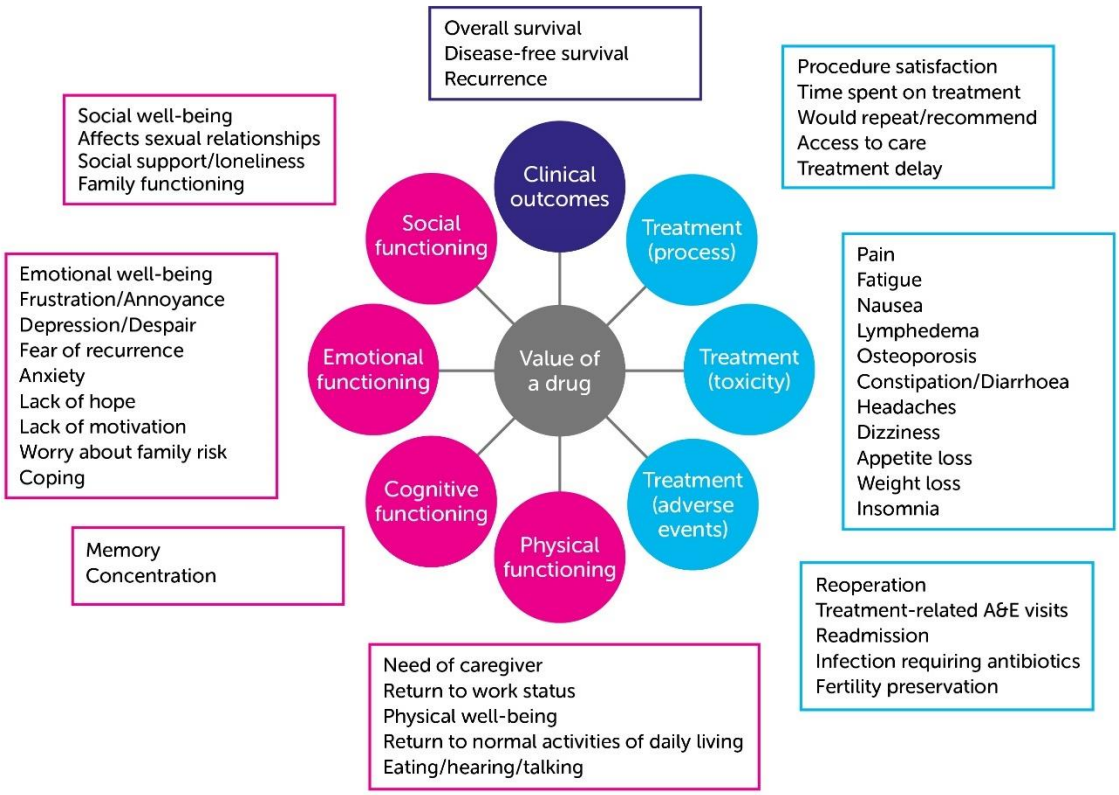
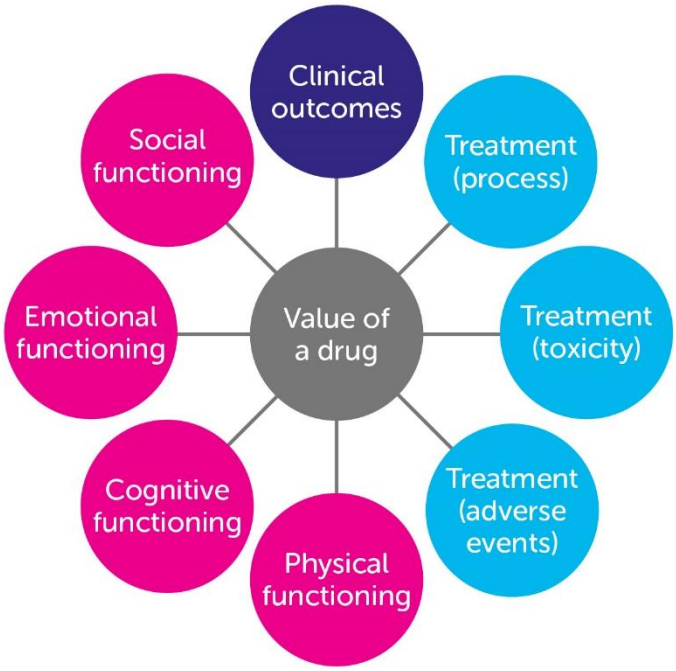


Table 3: Outcomes flower petal definitions

Petal	**Definition**
Clinical Outcomes	Measurable changes in indicators of health as a result of a given treatment(s); *e.g. tumour growth*
Treatment (Process)	Outcomes related to the way in which treatment is provided; *e.g. time spent on treatment*
Treatment (Toxicity)	Outcomes related to the harmful clinical effects of a given treatment(s); *e.g. headaches*
Treatment (Adverse Events)	Outcomes related to any untoward medical incident or event as a result of a given treatment(s); *e.g. treatment related A&E visits*
Physical functioning	Outcomes related to the ability of an individual to undertake basic and more complex activities; *e.g. return to work status*
Cognitive functioning	Outcomes related to the ability of an individual to undertake intellectual activity; *e.g. memory, concentration*
Emotional functioning	Outcomes related to the feelings of an individual; *e.g. anxiety*
Social functioning	Outcomes related to the ability of an individual to interact in everyday environments such as work, social activities, relationships etc.; *e.g. loneliness*

Figure 2: Outcomes flower (simple)



Confirming the framework

To confirm our outcomes framework, we considered the generic and cancer-specific measures reported in the papers reviewed and attempted to identify the 'best' measure which could capture the petals (and most of the outcomes). We could not find any outcome measure, including clinical outcomes, PROMs or PREMs, that encompasses all the elements. Cancer patients were then consulted to see if they could corroborate the outcomes framework.

During the discussion at the first focus group (with five cancer patients), each of the 'petals' in the outcome flower in Figures 1 and 2 was identified as important to one or more of the participants. Patients in the focus groups stated that life extension (survival), quality of life, side effects/toxicity, adverse events, the environment a medicine was administered in and the impact treatment with it has on family members were all key outcomes of importance.

Dependency of outcomes

As observed in the literature review, the degree to which these outcomes are important depends on the characteristics of the individual in question, the cancer they are being treated for, the drug they are receiving, the intention to treat, and other context specific factors. For example, patients in the focus group felt that clinical outcomes are relatively more important for older patients, whereas 'functioning' outcomes are relatively more important to younger patients. Another example of variability according to context is with respect to fertility preservation in the 'Treatment (Adverse events)' petal: one participant stated and others agreed that the potential treatment side effect of infertility "*would be considerably more important for a younger person, particularly if they did not have any children yet*".

The importance of the specific context within which a cancer medicine is given was also confirmed in several of our interviews with stakeholders and experts (Appendix 3). A clinician stated that when relating payments to outcomes "*Outcomes for adjuvant patients will be very different to those whose disease is metastatic*."

All stakeholders (patients, clinicians, commissioners, industry and academic OBP experts) were in agreement that outcomes of importance and/or their relative importance, should be expected to vary according to the specific cancer medicine, the cancer being treated, its site and stage. Consequently, no two OBP schemes may be the same.

Attribution of outcomes

The issue of attribution of particular outcomes to use of a specific medicine (i.e. causality) was discussed by the patients in the focus group, and also in the stakeholder interviews. While some patients were challenged when asked to only consider the outcomes of their cancer medicine, struggling to separate this from the outcomes of the continuum of cancer treatment, others questioned the causal link: "*it is very hard to find causality when considering [functioning outcomes from the outcomes 'flower']*".

In the stakeholder interviews it was taken as granted that any outcomes to be linked to price must be outcomes that are expected to be affected by the medicine, although the medicine may be only one of a number of factors affecting those outcomes. If the outcome of interest is not one that is typically collected in clinical trials then this introduces an additional challenge of determining effectiveness with real-world data.

Special consideration will need to be given to the comparator used in a real-world setting to determine the extent to which outcomes are attributable to treatment; this may include collecting data in patients not receiving treatment which would have resource implications.

A theme that came out of the first focus group discussion with patients was that they thought there was sometimes a misalignment between outcomes that are important to patients and outcomes that are important to clinicians and researchers. It was claimed that patients often don't report side effects because they worry it will lead to them being taken off treatment. The majority of patients at that focus group agreed that they would be willing to 'suffer' side effects if a medicine extended their life.

This and the attribution issue together imply that it may be preferable to give greater weight to clinical outcome measures in initial OBP schemes relative to patient reported outcomes when constructing an aggregate outcome measure (the third step in implementing OBP as put forward by Sussex et al.). When looking to test feasibility of OBP in the NHS, this will allow for an OBP scheme which is more easily auditable and therefore open to future investigation and inquiry. Once feasibility is established wider implementation would be possible with more weight given in future OBP schemes to patient reported outcome measures.

Objectivity of outcomes

The objectivity of measured outcomes was specifically mentioned as important by some of the stakeholders interviewed. There were strong opinions regarding the need for objective outcome measures that – as described above – can be clearly linked to use of the medicine. As one expert stated: *"If outcomes are not objective then the system can be gamed."*

While quality of life outcomes were deemed important by the stakeholders interviewed, there was a preference for well-validated, objective outcome measures (*"The more subjective the outcome the more difficult it is to capture"),* including survival.

Framework of outcomes most important to patients

To further support Sussex et al.'s first step in implementing OBP we sought to identify which outcomes are most important to cancer patients when determining the success or otherwise of a medicine.

In the second focus group we found that life extension (survival), quality of life, and emotional functioning were important. This group of patients further confirmed that context matters; that outcomes are situation dependent and affected by a patient's diagnosis and care pathway. They also confirmed that causality can be problematic, with many of the outcomes being considered as not necessarily related to the medicine but rather to the cancer diagnosis itself.

To test the relative importance of different outcomes in a sample of patients and carers, and to explore the context issue and what it might mean for the choice of outcomes in an OBP scheme, an online survey was developed. The survey allowed us to consider how different experiences with cancer are associated with different preferences around treatment outcomes, and how different characteristics are associated with different preferences around outcomes in a sample of patients and carers.

Taken together, the 164 patients and carers who responded to the online survey ranked 'survival' and 'progression, relapse or recurrence of cancer' as the first and second most important outcomes respectively when considering cancer treatment options (see Box 4 for the full ranking; and Appendix 5 for the exact questions asked in the survey). This was regardless of a respondent's experience with cancer or their individual personal characteristics.

This reaffirmed the views of patients in the focus groups, with one participant in the first focus group stating "*how long I stay alive is the most important outcome for me*", and all participants in the second focus group ranking life extension as 'important' or 'most important'. Additionally, this aligns with the papers identified in the literature review (Appendix 2) that elicited patient preferences for different treatment outcomes: survival or being cured was deemed more important than quality of life or side effects.

Box 4 – Rank order of outcomes by patients

1. Survival
2. Progression, relapse or recurrence of your cancer
3. Long-term side effects
4. Return to normal activities of daily life
5. Short-term side effects
6. Emotional wellbeing
7. Satisfaction with treatment
8. Impact on family and caregivers
9. Re-surgery
10. Fertility problems

In the majority of subgroups of respondents analysed (grouped by specific cancer experience or personal characteristics), long-term side effects was ranked as the third most important outcome, with return to normal activities of daily life fourth. There was, however, one instance where the respondent's characteristics affected their ranking of outcomes: on average those with lung cancer ranked returning to normal activities above long-term side effects.

There were also some differences between respondents according to whether the purpose of their medicine was cure or merely control of the cancer. While the top two outcomes were the same regardless of treatment intent, those patients receiving medicines to control or manage their cancer ranked returning to normal activities above long-term side effects, and emotional wellbeing above short term side effects. But patients (and their carers) who had received (or were receiving) medicines to cure had ranking more similar to those in Box 4.

This aligns with the earlier work of Minion et al.[39] who considered the preferences of ovarian patients and how they differ with treatment intent. The heterogeneity of response across patients with different experiences further confirms the context-specificity issues identified in the qualitative components of the project.

Given the literature review, insights from patients in the focus groups and the findings from the patient (and carer) survey, a core set of outcomes that could form the basis of an outcomes framework for an OBP scheme in the NHS are:

- Survival
- Progression, relapse or recurrence of your cancer
- Long-term side effects
- Return to normal activities of daily life.

Depending on the cancer and the stage it has reached, the treatment characteristics and the patient population, other outcomes from the long list may be important and could form part of a framework for OBP.

Whatever set of outcomes is chosen as the basis for OBP for a new cancer medicine, they can be expected to overlap with the outcomes that combine in the estimation of cost per QALY cost effectiveness ratios in the evidence considered by NICE. But OBP creates the opportunity to take different combinations of outcomes into account when determining how much a medicine's supplier is paid.

Metrics and measurement

The second step necessary for implementing OBP[14] requires consideration of the metrics for each outcome measure. While clinical measurement is less ambiguous than patient-reported outcomes, defining for example cancer progression and progression-free survival is not without problems. Progression can be subjective in terms of the degree of tumour growth, and assessment of time to progression for progression-free survival estimates requires regular monitoring. Although such monitoring may happen in clinical trials that may not necessarily happen in standard practice.

This also raises the issue of timing and when to measure outcomes. Outcomes achieved a long way in the future add an additional layer of complexity to the negotiation of prices and payment arrangements. OBP schemes will need to specify when outcomes are to be measured; as noted by a commissioner we interviewed:

> *"There would be complications around time lags for the outcome of interest. It is easy to work in a system where payment is made upon prescription. If payment is delayed until such a point that an outcome is achieved (or not), that would add huge uncertainty."*

Only one paper reviewed[40] shows a full description of value-based outcome metrics, for breast cancer. The authors extract a list of outcomes from a systematic literature review, and use focus groups to select the most important outcomes for breast cancer. The authors provide a full description of how these outcomes could be valued, and the full process through which value-based measures as well as dynamic capture of these metrics would be developed. The important issues identified in our research (such as time points, patient population, or data source) are also included in the full description of the outcomes.[40] Further information can be found in Appendix 2.

4.2 Linking Outcomes to Price

Across the 13 interviews conducted there was frequent support for, and no opposition to, the idea that OBP is a potentially desirable option where there is significant uncertainty about the outcomes that medicines will achieve in practice (see Appendix 3).

Schemes are heterogenous in their design

Several different types of OBP schemes were identified in the literature (see Appendix 1) and there are numerous instances of those schemes being used in a range of countries internationally including Australia, Italy and the Netherlands. The existence of OBP schemes globally, including previous experiences in the UK, suggests that wider implementation of OBP in the NHS is possible.

The OBP schemes reported in the literature were heterogeneous in their design. They varied by geographical location, payer type, medicine and disease area, outcomes and how measured, how the outcome data are captured, and the relationship between medicine price and outcomes. Some were for cancer drugs, but medicines for many different diseases have been the subject of OBP schemes.

Outcomes employed

Clinical outcomes were favoured as the basis of the large majority of OBP schemes, i.e. outcomes recorded by clinicians during the treatment process to monitor the extent to which patients are responding to treatment. The specific clinical outcome or outcomes used in an OBP scheme depend(s) on the particular cancer, or other disease, and stage of treatment for which the medicine is being used.

Other types of outcomes measured in OBP schemes were:

- survival rates;[25 26 30]
- adherence to treatment;[20 27]
- hospital admission rates,[20 23]
- re-admission rates; [28]
- side-effect profiles;[31]
- quality of life, although it is unclear which specific measure was used;[31] and
- patient reported outcome measures, such as the Asthma Control Questionnaire (ACQ-5).[26]

Garrison et al.[20] noted that side-effect profile and patient experience was collected among the 26 schemes in the Netherlands, although it is unclear in exactly how many this took place.

It is worth noting that many schemes measure more than one outcome, for example collecting clinical data alongside information on medical adherence. This necessarily adds to the administrative burden of running the OBP scheme, but it enables a more nuanced view to be taken of the degree of success being achieved for patients by the medicine concerned.

Data collection and timing

In many cases the outcome data were collected and managed in patient monitoring registries. The most prominent example of this was in Italy, where, for example, the Cancer Drug Registry covers around 100,000 oncology patients in an attempt to monitor patient eligibility, determine utilisation in clinical practice and collect the necessary clinical outcomes.[20]

A similar approach was taken in a Catalonian OBP scheme, with data on progression collected using an electronic prescribing system.[32] In Australia, a patient registry system was set up in the Bosentan scheme for those with pulmonary hypertension to track survival and mortality rates among patients.[25] [26] Thus a registry-based approach to collecting data is evidently feasible.

The length of time that elapses between treating a patient with a medicine and measuring the outcomes that achieves also varies from scheme to scheme and is potentially very important. In the words of one of our interviewees:

> *"If quality of life data are collected to inform price on an individual-basis, the time points for data collection (whether during treatment, shortly after, or post recovery) become very important and will have a huge impact."* (Clinician/commissioner)

For example, outcomes were considered after three months in the Adalimumab scheme for rheumatoid arthritis in Australia.[25] Whereas at the other extreme, data came from a 10-year observational study for the UK multiple sclerosis scheme.[29]

Relationship between outcome(s) and price

The literature review found that the relationship between outcomes and the price and/or reimbursement of the medicine varied considerably in the different OBP schemes. In some instances the scheme was a cost sharing arrangement where the manufacturer reimburses the payer in full in instances where the patient does not respond to the medicine.

Other risk-sharing arrangements were also evident, where manufacturers face a reduced price for initial treatment cycles until it is clear whether a patient is responding to the medicine. There was also evidence of outcomes guarantees or pay-for-performance schemes, where the manufacturer provides rebates, refunds or price adjustments if the medicine fails to meet pre-agreed outcome targets.

The review also identified OBP schemes where price is indirectly, rather than directly, linked to the outcomes achieved by the drug. Coverage with Evidence Development (CED) is one example of this, where access to a drug is initially provided on the condition that further population-level evidence is gathered. Based on this further evidence the payer then makes a binary decision whether to continue funding the medicine for all patients or for none. The CDF in England has this form. Another variant of the same approach is conditional treatment continuation, which applies the same conditions as CED but is based on individual rather than population level data.

Simplicity

While the stakeholders in their interviews did not converge on any particular preferred type of payment/pricing scheme (see Appendix 3), all agreed that it should be simple to operate with a clear link between the use of the medicine and the outcome. A clinician with commissioner experience noted that: *"From experience, companies begin the process with good intentions to implement novel pricing arrangements, but generally end up falling back on a simple discount when the practicalities and implications are fully thought through."*

To quote one of the experts interviewed: *"We need to make outcome-based pricing schemes as simple as possible if we are to overcome the barriers."* In other words, experience suggests that an OBP is viable if it is not too burdensome to implement. Burdens particularly relate to the need to collect and monitor outcomes data, which is discussed further below.

4.3 Implementing OBP in the NHS

Among the stakeholders interviewed, many were in favour of, and none was opposed to, having OBP schemes in the NHS (see Appendix 3). However, taken together, the interviewees' responses did not converge on any particular preferred type of OBP scheme, other than a common view that it should be simple and based on objective outcome measures that are clearly linked to use of the medicine.

Collectively the interviewees held the view that such schemes were desirable when there is significant uncertainty about the outcomes that medicines will achieve in practice. There appeared to be a shared eagerness to undertake OBP in the NHS: government and industry are showing willingness and the clinical community accept there is a need:

> *"It is … our responsibility to find a way – which is sustainable and affordable – of bringing promising therapies forward." (Government)*
>
> *"Don't ask whether outcome-based pricing should be done; ask how it can be done." (Industry)*
>
> *"Outcome-based payments for cancer drugs would be beneficial for society" (Clinician)*

Both the literature review (see Appendix 1) and the interviews (see Appendix 3) revealed that OBP schemes are not without difficulties in terms of implementation but that these are, or should be, surmountable.

Challenges in using observational data

Data collected via registries and observational studies may be of poor quality, which hinders comparisons with clinical trial evidence. A further difficulty with observational data is that, unlike RCTs, where treatment effect can be isolated, confounding factors (that are not always observable) complicate the measurement of outcomes and the direct attribution of the outcomes to the drug.

As noted by an expert we interviewed, it was difficult to agree on the level of reimbursement for an OBP scheme in Australia for a pulmonary artery hypertension medicine because the real-world casemix (the group of patients under consideration, to whom the intervention has been provided) was different to that in the trial. Thus it wasn't clear if the observed outcome differential was due to differences in the performance of the drug in the real world, or to differences in the casemix of people being treated with it.

These issues reflect that there can be a difference between efficacy as established in clinical trials ('can the drug work under ideal conditions'?) and effectiveness ('does the drug work in a real-world health care environment'?). The size of this efficacy-effectiveness gap is what drives the need to generate real-world evidence, and what makes OBP a potentially attractive option for some medicines. OBP provides the opportunity to ensure payment is aligned with effectiveness in the real world, but issues such as the casemix and difficulty in attributing outcomes to a specific drug represent barriers to realising this potential in some cases.

It is sometimes a challenge to collect sufficient real-world data rapidly enough to be useful as the basis of OBP. In three Swedish CED schemes and the English multiple sclerosis scheme, it took longer than expected to recruit sites and patients for the necessary observational studies, which delayed the gathering of good quality evidence and hence the ability to adjust price on the basis of outcomes.[30]

In the extreme case of the OBP scheme for MS medicines in England, the delay was so long that new and improved drugs had been launched before the scheme could influence the prices of the scheme medicines.[41] However, the majority of schemes reported in the literature were not identified as having this problem.

It is important to acknowledge that many OBP schemes also draw on ongoing (global) trials to assess effectiveness. OBP schemes therefore do not have to solely rely on observational data. The type of data will depend on the issue, i.e. the uncertainty, that the scheme is attempting to resolve.

Resource requirements and workforce burden

Other barriers identified in the literature included administrative burden and funding gaps regarding the additional data collection that is often required. OBP schemes will, to varying degrees, require data collection, data sharing and data analysis by NHS staff.

This proved to be a particular issue for the risk-sharing arrangement for beta interferons and glatiramer acetate to treat MS in England. This scheme highlighted the challenges of data collection, data analysis and data governance. In this instance not all patients receiving treatment were in the study cohort, additional nurses had to be hired to enable the scheme to operate and the academic team tasked with monitoring outcomes withdrew due to governance concerns.[41]

To quote one of the clinicians interviewed, the general issue is that: *"Anything is measurable given sufficient resource. The difficulty is in managing how and who collects the data, and ensuring there is sufficient resource to support."*

Data infrastructure

There was a recognised need across all stakeholders for data infrastructure in the NHS to support OBP, but opinions differed regarding whether and to what degree such infrastructure already exists and is being used.

One industry stakeholder stated that *"the lack of [data] infrastructure in the NHS is an issue*", while another industry stakeholder said *"outcome-based pricing is more of a reality in oncology than other areas, due to the data that is being collected at the moment, e.g. SACT* [the Systemic Anti-Cancer Therapy dataset]*"*, which was partly confirmed by a stakeholder from government who took the view that "*The infrastructure is there."*

Should OBP schemes be implemented, there are a range of national datasets, described in Appendix 6, that could be sources for various of the possible outcome metrics.

Key is Public Health England's National Cancer Registration and Analysis Service (NCRAS), which has records of every cancer patient diagnosed in England, submitted against the Cancer Outcomes and Services Dataset with linked records from the National Radiotherapy Dataset, and the Systemic Anticancer Therapy (SACT) dataset (which covers all treatments that have an anti-cancer effect relating to chemotherapy, including hormones and bisphosphonates, oral chemotherapy, intravesical chemotherapy and targeted / biological therapies).

These data can be linked to activity data via Hospital Episode Statistics (HES) and death data via the Office of National Statistics (ONS). The SACT database (with its linkages) remains one of the most notable datasets in the world with huge potential for real-world data analytics. Specifically with respect to OBP schemes the data maturity allows survival studies in relation to treatment of certain poor prognosis cancers (from analysis of 30-day mortality) but not yet those of good prognosis populations (those with longer survival expectations whose potential short-term treatment side-effects are not fatal).

Beyond data capabilities, a further implementation issue relating to the nature and timing of relevant outcomes for cancer drugs is that it may be difficult to negotiate payment arrangements that are predicated on outcomes achieved a long way in the future. Moreover, the ability to link to real-world adverse events (particularly those that happen in hospitals aside from the cancer treating facility) remains limited, but is improving.

National cancer audits, coupled to investments from Health Data Research UK and increased health systems research initiatives (such as Bowel Cancer Intelligence UK (BCI UK) at Leeds University), should support further improvements. Having a consistent definition of cancer progression and recurrence is key to supporting OBP schemes that are implementable and acceptable to all parties; definitions of these parameters currently vary between datasets. Better linkage using proxy and indirect identifiers, better coding approaches, and high-resolution validation studies also have the potential to increase the value of health and cancer care data in the UK, which could expand the possibilities of OBP schemes in the NHS.

Institutional arrangements

In addition to resource constraints and the current NHS data infrastructure, other challenges to implementing OBP were identified concerning institutional factors and financial/fiscal rules. These challenges are in principle surmountable, but they would require changes to current arrangements.

For example, Government and industry have agreed a new 5-year Voluntary Scheme for Branded Medicines Pricing and Access, which committed to increasing commercial flexibilities for products which offer the best value to the NHS, but also indicated that a simple discount would be preferred in most cases. Value Added Tax (VAT) rules create their own complication around rebates (hospitals pay VAT when they buy medicines, but do not get the VAT refunded if the manufacturer later makes any refunds).

The financial cycles of the NHS also have implications:

> *"Ideally the outcomes on which to optimally base price would be long-term clinical endpoints. But government accounting rules and NHS England funding cycles makes this impossible. Even two to four years would not be realistic. Therefore this timeframe element needs to be an important consideration in the outcome of choice, on top of what is clinically most relevant."* (Government)

That said, there are also enablers of OBP, as well as challenges to it. Alongside the existing data infrastructure, the main enabler to OBP is a shared recognition by patients, clinicians, NHS and industry of the potential importance of such pricing arrangements to enable access to new cancer medicines.

5 Conclusions and Recommendations

5.1 Outcome-Based Payment Schemes are Feasible when there is Uncertainty

Information has been collected from a range of sources – the literature, patients, stakeholders and experts – to assess the practicality of making OBP for some cancer medicines a reality in Greater Manchester and the wider NHS. Our conclusions must be seen within the constraints of the limited numbers of interviews and patient/carer survey respondents, and the non-random nature of the latter sample. Nevertheless, we have found that OBP schemes have a role in many healthcare systems internationally and their use in the NHS was supported by the stakeholders interviewed.

OBP is of most relevance where substantial uncertainty remains about the effectiveness of medicines even after the completion of clinical trials, by providing the opportunity to ensure payment is aligned with effectiveness in the real world. In such cases, linking the reimbursed price of a medicine to the outcomes actually achieved in practice could make it possible for patients to have access to the medicine sooner than would otherwise be possible, since healthcare payers may not be willing to commit to reimbursing the medicine's price in full unless they have evidence that it works in practice as well as it did in the clinical trials.

Several different types of OBP schemes were identified in the literature along with numerous instances of those schemes being used in a range of countries internationally including Australia, Italy and the Netherlands. The existence of OBP schemes globally, including previous experiences in the UK, suggests that wider implementation of OBP in the NHS is possible.

Collecting real-world outcomes data is not without its challenges and entails some costs in terms of staff time. But data challenges and costs are worth taking on when the prize for doing so is big enough. The size of the prize depends on the potential value of the medicine if it works and the degree of uncertainty that remains (despite the clinical trials) about the outcomes that will be achieved in practice in the NHS for some or all patient subgroups. The bigger the potential benefit and the greater the uncertainty about whether, or for whom, it will be achieved in practice, the more attractive OBP becomes.

OBP is likely to be desirable for some but not all new medicines. Where it could be desirable is where a more traditional payment approach cannot be agreed upon between NHS England and the manufacturer of the medicine, but where there is a reasonable, if uncertain, prospect of it being proven to be sufficiently beneficial to justify reimbursement once more is known about its effectiveness in real-world practice.

5.2 The Outcomes Framework should include Clinical and Quality of Life Measures

Our analysis of cancer patients' and their carers' views on the outcomes of greatest importance to them shows that they prioritise survival above all other outcomes, and that the next most important outcome is avoiding the progression, relapse or recurrence of the cancer. These are objective, 'hard' outcomes, which are possible to measure and record.

Mortality data are already recorded and are linkable to data on patients' treatment in hospital. Information on disease progression could similarly be collected consistently across the country. The NCRAS and SACT show that the infrastructure exists, though data are not always complete, but data quality and completeness is improving over time and research is ongoing.

Other outcomes are important too, if not quite as much as survival and halting disease progression. The avoidance of unpleasant and persistent side-effects and the ability to resume the normal activities of their daily lives are the outcomes next most highly valued by patients. These outcomes would not currently be captured in routine clinical practice. Measuring them and linking them to the price of a medicine are more problematic, but not impossible.

A clear challenge is that measurement of such quality of life related outcomes needs to take place over a sustained time period not only during but also after the treatment with the medicine. Measuring such outcomes would require additional data to be collected and recorded, for example in an extension of the SACT database (which currently records mortality but no other patient outcomes), and that would require NHS staff time.

There was some discussion among our interviewees about the objectiveness of quality of life measures, but there are numerous well-validated instruments in existence. The particular dimensions of outcomes of most importance will vary from medicine to medicine, depending on the nature of the treatment, the nature of alternative existing treatments, the cancer being treated and its stage. Selecting and agreeing on an appropriate instrument for a given medicine or patient group and then ensuring it is consistently administered are both feasible but require effort.

Outcome measures that are seen to be too subjective or/and are susceptible to too many factors beyond the cancer medicine alone will likely not be acceptable to one or both of the parties (NHS and pharmaceutical company) negotiating the OBP scheme. A scheme that would be costly to administer, in terms of staff time to input data and ensure its accuracy and completeness, will not get off the ground. Thus the watchwords for a successful OBP scheme are 'objectivity' and 'simplicity'.

In the first instance this suggests, for simplicity, concentrate on one or more medicines with relatively small patient groups where it would be possible to agree what it means for a patient to have responded positively to treatment, in terms of survival and disease progression. More elaborate schemes, for larger patient groups and with more weighting on outcome types related to long-term side effects and the ability to return to normal daily activities, might be contemplated later.

In short, the challenge of designing and negotiating an OBP scheme appears worth tackling where the alternative would be a potentially cost-effective medicine not being available to NHS patients, or the NHS paying for a medicine that did not work as expected in the real-

world patient population. As previously noted, the CDF in England also provides a solid foundation for the more routine use of OBP schemes for some cancer medicines.

Our recommendations on the basis of our overall analysis and in line with these conclusions are set out below.

5.3 Recommendations

Box 5 – Recommendations

- GMHSCP, Government, NHS England, the pharmaceutical industry, NICE and all other relevant stakeholders should continue to explore the use of OBP schemes, with the aim of facilitating patient access to cancer medicines in cases where a simple discount on the medicine's list price cannot be agreed on a timely basis. Conversations should be taken forward on a joint basis, through forums and initiatives such as the Accelerated Access Collaborative.

- GMHSCP, Cancer Research UK, NHS England, NICE and the pharmaceutical industry should work together to horizon scan medicines nearing regulatory submission which might be suitable for an OBP scheme. We believe such medicines would have the following characteristics:
    - Potentially large benefit to patients receiving the medicine
    - Small to moderately-sized patient populations
    - Immature clinical trials data
    - A disease profile where improvements in outcomes measurable in the short-term (including overall survival and non-progression/relapse) are particularly valuable.

- NHS England or NICE should publish information on how outcomes are measured and linked to price in any OBP schemes for medicines in operation in the NHS. This should stop short of publishing commercially sensitive financial information.

- As part of any future OBP schemes negotiated between NHS purchasers of cancer medicines and manufacturers, specific metrics should be included to measure the drug's effects on patients in the NHS, on the following four types of outcomes as standard:
    - Survival
    - Disease progression, relapse or recurrence
    - Long-term side effects
    - Return to normal activities

- Future research into the use of OBP in the NHS should investigate with NHS staff the practicalities of collecting data for an OBP scheme, based on exemplar medicines and for measures of the four outcome types listed earlier.

- Future research into the use of OBP in the NHS should investigate the relative weights which should be attached to measures of the four “standard” outcomes (and potentially others) we wish to see included in future OBP schemes. This should include seeking the views of patients and other key stakeholders. This research should also clarify options for linking outcomes to a drug’s price in practice.

- As part of future research into the use of OBP in the NHS, a mapping exercise should be undertaken to ascertain the appropriate data sources, and identify “gaps” in the capacity to collect data on the “standard” outcomes specified above. This review should involve NHS Trusts providing cancer care, Public Health England, NHS England and the pharmaceutical industry.

- NHS England and Public Health England should ensure resource is available within PHE to monitor and analyse in a timely manner the data submitted to SACT as part of any future OBP schemes adopted in the NHS nationally; and should explore the feasibility of using SACT or another consolidated database to capture all four “standard” outcomes, in order to facilitate their inclusion in future OBP schemes.

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Appendix 1 – Outcome-Based Payment Schemes Literature Review

Objective

A Rapid Evidence Assessment (REA) was undertaken in order to identify existing studies and descriptions of schemes that link the outcomes achieved by a medicine with the price or reimbursement paid by health care payers. A particular focus of the search strategy was to identify international examples of these outcome-based payment (OBP) schemes.

Furthermore, the review considered all disease areas, not solely cancer medicines. Thus we sought to identify as many past and current OBP schemes as possible in order to learn practical lessons that might help to design such a scheme to be applied to new cancer drugs purchased by the NHS in Greater Manchester and in England more widely.

Method

Like all systematic literature reviews, REAs take a replicable and transparent approach to searching and identifying the literature. However, unlike 'Systematic Reviews', which aim to search the entire evidence base, the scope of REAs is formally restricted through the search and screening criteria to identify the most relevant literature. The following paragraphs describe how that was achieved.

Criteria

OBP schemes are defined as medicine pricing or reimbursement agreements that link the price to the outcomes achieved by patients receiving the medicine in question. Our inclusion and exclusion criteria to identify the literature of most relevance are described below.

Inclusion criteria:

Meeting all of the following criteria:

- Specific OBP schemes for medicines, if they include:
    - Information on outcomes used in the scheme
    - Information on how these outcomes are measured
- Papers in English
- Research from or about any country
- Systematic reviews/REAs as well as original research
- Papers published between January 2007 and January 2018.

Exclusion criteria:

- Specific OBP schemes with no information on outcomes used
- Purely theoretical papers, only discussing the methodology of OBP schemes

- OBP schemes for health care services, systems, diagnostics, etc. (i.e. those that are not specific to medicines)
- Commentaries, editorials and features
- Papers published before January 2007.

Search strategy

Four separate reference and abstract databases were searched in order to identify the relevant literature:

- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- Web of Science
- PubMed
- Econlit

The following search terms were used to search the above databases. Papers were included that contained any one of the terms in parts A and any one of the terms in part B and any one of the terms in part C: AND/A-C

(A). Search terms for drugs:

1. medicine(s)
2. pharmaceutical(s)
3. drug(s)
4. episode(s)
5. treatment
6. technology
7. OR/1-6

(B). Search terms for pricing:

1. pric(*)
2. reimbursement(s)
3. payment(s)
4. OR/1-3

(C). Search terms for outcome-based schemes:

1. “outcome(s)-based” OR “outcome(s)-related” OR “outcome(s)-linked” OR “outcome(s)-specific”
2. “performance-based” OR “performance-related” OR “performance-linked” OR “performance-specific”
3. “value-based” OR “value-related” OR “value-linked” OR “value-specific”
4. “risk-based” OR “risk-related” OR “risk-linked” OR “risk-specific” OR “risk-sharing”
5. (“conditional coverage”) AND (outcome(s) OR performance OR value OR risk)

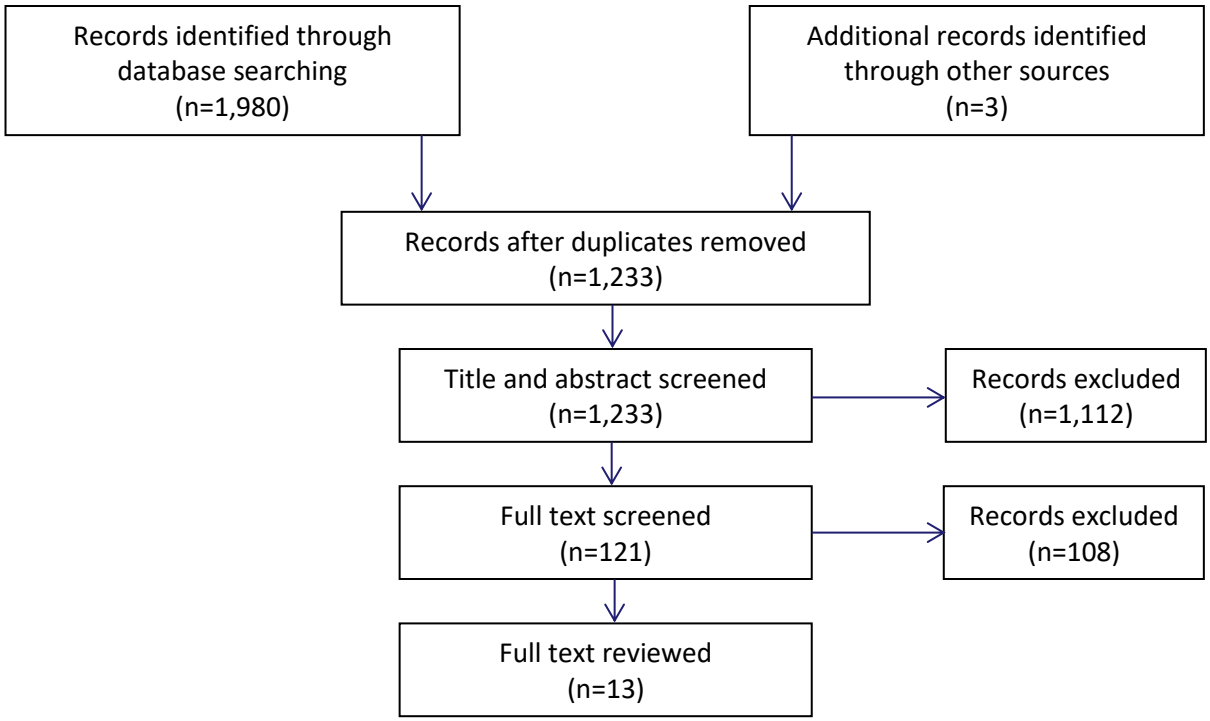
6. ("pay for performance") AND (outcome(s) OR performance OR value OR risk)
7. ("cost sharing agreement") AND (outcome(s) OR performance OR value OR risk)
8. ("evidence development") AND (outcome(s) OR performance OR value OR risk)
9. ("risk-sharing") AND (outcome(s) OR performance OR value OR risk)
10. ("payment by result(s)") AND (outcome(s) OR performance OR value OR risk)
11. ("managed entry agreement") AND (outcome(s) OR performance OR value OR risk)
12. ("patient access scheme") AND (outcome(s) OR performance OR value OR risk)
13. ("flexible pricing") AND (outcome(s) OR performance OR value OR risk)
14. OR/1-13

Finally, additional literature was identified in discussion with the project Steering Group, as well as through contact with experts in the field.

Search outputs

Figure 3 provides a graphical representation of the literature identified in the search, and the outcome of each stage of the sifting process. Titles, abstracts and full texts were reviewed by two researchers (JP and MY). A random sample of 50 papers were screened by both researchers to ensure the inclusion/exclusion criteria were applied consistently.

Figure 3: PRISM flow diagram



A total of 1,983 individual records were identified in the initial search (1,980 from the database search and three additional papers identified by members of the Steering Group). Removing duplicates left 1,233 unique papers. The title and abstract of each paper were then scanned to exclude articles outside the scope of the review and selected 121 potentially relevant articles as a result.

After full text screening, a further 108 papers were excluded, one of which was excluded because access to the full text could not be obtained. This left 13 papers for full text review, which provided information on OBP schemes internationally.

Data extraction

Data from the 13 papers identified for full text review were extracted by the same two researchers who screened the literature (JP and MY). To ensure consistency in their approaches both researchers extracted data from one randomly selected paper and compared the results. Data extraction from all other papers was by one or other of the researchers. Where available, information was extracted into a standardised template on the following items:

- Scheme: name of scheme and partners involved
- Payer type: public and/or private
- Introduction year
- Type of OBP scheme: cost-sharing, payment-by-results, risk-sharing, coverage with evidence development, outcomes guarantees, conditional treatment continuation, etc.
- Drug and target population
- Outcomes linked to price
- Relation between outcomes and price
- Method of collecting outcome data
- Barriers to collecting outcome data.

Findings

Summary of the literature review

In the 13 papers subjected to full text review, a large number of OBP schemes were identified. In some cases specific schemes were referred to in multiple papers. Overall, references were found to 86 separate schemes – i.e. outcomes-related pricing / reimbursement arrangements for a medicine or group of medicines in a geographically defined health care system.

The number of schemes existing, or having existed, will probably be greater than 86 as individual references are inevitably constrained by the date at which the information they contain was gathered. Likewise, some schemes may not have been identified by the literature review, and other schemes may exist that have not been reviewed, evaluated or publicised. Despite this, the range of OBP scheme types represented in the 86 examples is already broad, with a wide range of contexts also represented. The findings of the literature review are outlined in the following paragraphs.

Results of the literature review

The results of the literature review are considered in terms of the geographical location and date of the scheme, the type of payer involved, the medicine and disease area the scheme relates to, the outcomes measured, how the outcome data are captured, the relationship between the price and outcomes, and any barriers to implementing such schemes that are mentioned.

Extent of OBP schemes used to date

OBP schemes were identified in a total of eight different countries, spanning three continents, as follows:

- 26 in the Netherlands,[20]
- 25 in Italy,[20-24]
- 17 in Australia;[25 26]
- Six in the US,[20 21 27 28]
- Four in France,[20 23]
- Four in the UK,[20 21 23 27 29]
- Three in Sweden,[23 30 31] and
- One in Spain.[32]

The earliest identified scheme was established in 2000,[26] with the most recent starting in 2012.[24] However, the majority of papers provided no information on the inception year of the schemes they discussed.

The vast majority (80) of the OBP schemes involved public payers for the medicine; e.g. the NHS in the UK,[20 21 23 27 29] the Pharmaceutical Benefits Scheme in Australia,[25 26] and the Italian Agency for Medicines in Italy.[20-24] Only the six schemes in the US involved private payers, such as private healthcare insurers.[20 21 27 28]

A great variety of medicines were included in the identified OBP schemes, treating numerous medical conditions. There were 18 schemes related to cancer, with 15 of these in Italy alone.[22] However, the authors did not go into detail about the types of cancer or the medicines used to treat them. In Australia an OBP scheme was used for imatinib, dasatinib and nilotinib in the treatment of the chronic phase of chronic myeloid leukaemia.[26] An OBP scheme was also used for gefitinib in the treatment of advanced EGFR-mutation positive non-small-cell lung cancer in Catalonia, Spain.[32] The UK implemented an OBP scheme for Velcade in the treatment of multiple myeloma.[21 27]

The remaining 68 schemes involve medicines treating conditions other than cancer, including: multiple sclerosis,[20 21 23 27 29] diabetes,[20 27] schizophrenia,[20 23] Parkinson's disease[31] and many more.

Outcomes measured

Viewed overall, a large number of outcomes are measured in the OBP schemes and used to determine the price and/or reimbursement of the medication. As many as 75 of the schemes involved measuring clinical outcomes to determine disease progression. One of these schemes took place in Catalonia, Spain,[32] two in Sweden,[30 31] four in the UK,[20 21 23 27 29] and five in the US.[20 21 27 28] In Italy all 25 OBP schemes appear to measure clinical outcomes.[20-24] Garrison et al.[20] reported that clinical outcomes are collected in the Netherlands, but it is unclear whether all 26 of these schemes measure clinical outcomes.

Different clinical outcomes are measured across the schemes, depending on the medicine and disease area. For example, the proportion of Philadelphia positive bone marrow cells and peripheral blood BCR-ABL levels were measured in the OBP scheme for imatinib, dasatinib and nilotinib in the treatment of the chronic phase of chronic myeloid leukaemia in

Australia.[26] In the UK Velcade scheme for the treatment of multiple myeloma, levels of serum M proteins were measured to determine progression.[21 27] Further, the Expanded Disability Status Scale (EDSS) scores of patients were measured in the UK multiple sclerosis scheme.[20 21 23 27 29] HbA1c levels were measured in schemes relating to obesity and diabetes,[21 30] as well as blood glucose levels among diabetes patients in the US.[27]

Beyond clinical measures, measured outcomes include: two schemes collecting survival rates;[25 26 30] three schemes collecting information on medical adherence;[20 27] two schemes collecting information on hospital admission rates,[20 23] with another measuring hospital re-admission rates;[28] one scheme measuring side-effect profile;[31] one scheme measuring quality of life, although it is unclear which specific measure was used;[31] and five schemes in Australia collecting patient reported outcome measures, such as the Asthma Control Questionnaire (ACQ-5).[26] Garrison et al.[20] noted that side-effect profile and patient experience was collected among the 26 schemes in the Netherlands, although it is unclear in exactly how many this takes place.

It is worth noting that many schemes measure more than one outcome, for example collecting clinical data alongside information on medical adherence.

Data sources for outcome measures

Several types of data sources are used to measure and collect the outcome measures referred to above. Not all papers detailed how the measures were collected but of those that did 57 schemes undertook observational studies, collecting real-world data through the tracking of patients receiving the medicine.[20-28 30 31]

In many cases the data from such observational studies were collected and managed in patient monitoring registries. The most prominent example of this was in Italy, where, for example, the Cancer Drug Registry covers around 100,000 oncology patients in an attempt to monitor patient eligibility, determine utilisation in clinical practise and collect the necessary clinical outcomes.[20] A similar approach was taken in the Catalonian OBP scheme, with data on progression collected using an electronic prescribing system.[32] In Australia, a patient registry system was set up in the Bosentan scheme for those with pulmonary hypertension to track survival and mortality rates among patients.[25 26]

When the data are collected

The length of time that elapses between treating a patient with a medicine and measuring the outcomes that achieves also varies from OBP scheme to OBP scheme. For example, outcomes were considered after three months in the adalimumab scheme for rheumatoid arthritis in Australia,[25] whereas data came from a 10-year observational study for the UK multiple sclerosis scheme.[29] In the Netherlands sufficient real-world data needed to be collected within four years of the drug receiving initial access, although it is unclear specifically how many schemes this applies to.[20] A similar approach was taken in two Swedish schemes,[23 31] with the real-world data collection occurring over two years.

Relationship between outcomes and payment

The relationship between outcomes and the amount paid for a medicine varies considerably across the identified OBP schemes. The 86 schemes identified in this literature review were categorised based on definitions provided in Garrison et al.,[20] outlined in Table 4.

Table 4: OBP scheme categories and definition

Scheme category	Definition
Cost sharing arrangements	Price reduction for initial treatment cycles until it is clear whether a patient is responding to the medicine.
Payment-by-results	Manufacturers reimburse the payer in full in instances where the patient does not respond to the treatment.
Risk-sharing	Manufacturers reimburse a proportion of the cost of the medicine for non-responders, often half of the cost.
Outcomes guarantees/pay-for-performance	Manufacturer provides rebates, refunds or price adjustments if the medicine fails to meet pre-agreed outcome targets at the individual patient level.
Coverage with evidence development	Access to a drug is initially provided on the condition that further *population level* evidence is gathered. Based on this further evidence the payer then makes a binary decision whether to continue funding the treatment or not.
Conditional treatment continuation	Payment for the continued use of a given drug is based on intermediate endpoints at the individual patient level.

One category of OBP schemes is cost-sharing arrangements, where there is a price reduction for initial treatment cycles until it is clear whether a patient is responding to the medicine (i.e. manufacturers provide a discount at the beginning of treatment). All four schemes in France adopted this approach.[20 23]

Another form of scheme is payment-by-results, where manufacturers reimburse the payer in full in instances where the patient does not respond to the treatment. This approach was taken in Catalonia, Spain,[32] across the six US schemes,[20 21 27 28] and in two of the UK schemes.[21 27]

Under risk-sharing schemes manufacturers reimburse a proportion of the cost of the medicine for non-responders, often half of the cost. The multiple sclerosis scheme in the UK is an example.[20 21 23 27 29]

Outcomes guarantees, also known as pay-for-performance, are schemes where the manufacturer provides rebates, refunds or price adjustments if the medicine fails to meet pre-agreed outcome targets at the individual patient level. An example of this is was the Velcade scheme in the UK, used in the treatment of multiple myeloma.[21 27]

The 25 Italian schemes are made up of cost sharing agreements, payment-by-results and risk-sharing agreements.[24]

Other types of OBP schemes also exist, where price is only indirectly linked to the outcomes achieved by the drug. Coverage with evidence development (CED) is one example of this, where access to a drug is initially provided on the condition that further population level evidence is gathered. Based on this further evidence the payer then makes a binary decision whether to continue funding the treatment or not, at an agreed upon point in the future. The

new Cancer Drugs Fund (CDF) in England is one example of this, although it was not identified through our literature review.

All 26 of the schemes in the Netherlands were CED schemes,[20] as well as all three of the Swedish schemes,[23 30 31] and two in Australia.[25 26] Conditional treatment continuation schemes, where payment for the continued use of a given drug is based on intermediate endpoints, were only identified in Australia, but represent 15 of the schemes there.[25 26]

Barriers to implementing OBP schemes

Numerous papers discussed the barriers to implementing OBP schemes in the real world, allowing lessons to be learned for any future attempt at setting up an OBP scheme in the NHS. In the CED scheme for Bosentan in Australia, for patients with pulmonary hypertension, the results from the patient registry were difficult to interpret [26] owing to the particular casemix recorded. That is, the mix of patients treated in the real world did not exactly match the mix of patients for whom outcomes had been recorded in the clinical trials of the medicine. In particular, observed survival was lower than expected as patients were older and had more advanced conditions than those in the clinical trials, making comparison with the clinical trial evidence challenging.

In the three Swedish CED schemes and the English multiple sclerosis scheme, it took longer than expected to recruit sites and patients for the necessary observational studies, which delayed the gathering of good quality evidence.[30] Additionally, it was administratively costly to undertake the numerous cost effectiveness reviews that were necessary throughout the scheme.[31] Finally, in the 26 CED schemes in the Netherlands the quality of the evidence collected in the real-world settings has been reported as poor.[20]

Barriers to implementation were also raised with respect to payment-by-result schemes. In the Catalonian scheme for gefitinib to treat patients with advanced EGFR-mutation positive non-small-cell lung cancer, data recording problems and administrative errors with the data led to legal disputes with the pharmaceutical company.[32] In two of the US payment-by-result schemes data collection and coordination at the health plan level was problematic.[27] Moreover, the observed patient outcomes could not be directly attributed to the drug itself.[27] This highlights a much wider issue with the observational nature of studies undertaken during OBP schemes.

In the outcomes guarantee UK Velcade scheme, for the treatment of multiple myeloma, issues were identified with the outcome measure of choice, serum M-protein. The clinical outcome was not considered a good enough proxy for life expectancy, with between 10-15% of patients not having measurable serum M-protein levels.[21] Beyond the outcome measure of choice, the patient tracking system was also deemed to be a burden, adding administrative complexity. This finding reinforces the importance of balancing administrative (including data collection) simplicity against the desire to measure particular outcomes.

Four of the 13 papers identified in this literature review discussed the barriers faced by the risk-sharing multiple sclerosis scheme in the UK.[20 21 27 29] Firstly, and as noted above, much like the Swedish schemes, it took more time than expected to recruit sites and patients for the observational study, in turn delaying the gathering of the necessary evidence. This was attributed to poor study design at the inception of the project.

As with the UK Velcade scheme, there were concerns about the selected patient outcome, as it is not easy to generate Health-Related Quality of Life (HRQoL) scores from the Expanded Disability Status Scale (EDSS) measure used. Further, no additional funding was provided to

account for the extra administrative burden on the local NHS commissioning organisations and hospitals collecting the data, and tensions arose around how best to undertake and maintain the running of the scheme due to the high number of stakeholders involved, all of whom had different interests. Finally, data collection for the scheme took so long that new and improved drugs had been developed before the scheme could influence price, undermining the whole scheme.

Several studies[21-23] highlight important barriers faced across the 25 Italian schemes. In particular, while it is important that non-responding patients are well documented in the patient monitoring registry, as those that are not documented will have to be funded by the payer as a success,[22] evidence suggests that compliance with the registry varies across regions, with around half of patients not included in some areas.[22 23]

Lu et al.[25] examined a variety of OBP schemes across the Asia-Pacific region, drawing conclusions about the more general barriers that such schemes face. The authors concluded that implementing OBP schemes is complex. Firstly, "detailed longitudinal information on patient clinical status" is required. Secondly, "substantial financial, human, and infrastructure resources" are necessary. Finally, OBP schemes "require a mechanism for adjusting price or level of reimbursement when explicit clinical endpoints are not met".

Conclusions

From the literature it can be concluded that OBP is certainly possible and has been considered worth attempting on numerous occasions, though not without problems. The literature review identified a considerable variety of OBP schemes, including for cancer medicines.

OBP schemes vary in terms of: geographical location, the payer type, the medicine and disease area, the measured outcomes, how the outcome data is captured, the relationship between the price and outcomes, and the barriers to implementing such schemes. There is no single 'best buy' OBP scheme to apply generally and there has been no widespread attempt to implement OBP schemes across a whole health care system. But there are numerous individual OBP schemes, especially in Australia, Italy and the Netherlands.

Appendix 2 – Outcomes Literature Review

Objective

A REA was undertaken in order to identify existing studies and descriptions of cancer treatment outcome measures. It was decided not to restrict the search to a particular cancer site, cancer stage, treatment or population. Similarly, the search did not focus uniquely on the patients' perspective, but embraced opinions about what is important to patients from alternative viewpoints such as health care professionals, general population and informal carers.

Method

Like all systematic literature reviews, REAs take a replicable and transparent approach to searching and identifying the literature. However, unlike 'Systematic Reviews', which aim to search the entire evidence base, the scope of REAs is formally restricted through the search and screening criteria to identify the most relevant literature. REAs therefore have the advantage of being quicker to produce results and less resource-intensive.

The search criteria were developed by AC, PL and PCM, and reviewed by JS and MY. Expert feedback was also obtained from Koonal Shah (Principal Economist, OHE). Attention was paid to the search criteria, trying not to impose a pre-existing structure to the findings. In this respect, care was taken with the wording of the search key words, avoiding using a potential outcome as an input for the search strategy. Titles, abstracts and full texts were reviewed by two researchers (PCM and AC).

Criteria

A series of initial online searches were run in order to inform our decision on the search criteria to be used for the REA. Different terms and combinations of terms were used to do an initial exploration of the literature. This piloting exercise pointed towards three areas identified as 'outcomes' in the health-related literature:

- Clinical Outcomes (COs), usually referred to as clinical endpoints, related to health and reported by clinicians. Papers following this interpretation of outcomes were more frequently found in the medical literature.
- Patient-reported outcomes (PROs), normally referred to as health-related quality of life (HRQoL) outcomes reported by the patient (not the clinician). This interpretation of patient outcomes is common in the health economics literature.
- Patient-reported experience (PRE), usually depicting non-HRQoL outcomes reported by the patient (not the clinician). This definition of patient outcomes is more recent and is closely related to the health services research literature.

The initial search also found that the number of papers published with different interpretations of outcomes has enormously increased since 2009. This increase in the outcome-related literature seems to align with the collection of new patient outcomes datasets and advances in technology including the increase in the use of tablets and

smartphones. In view of this, it was decided to focus on research published in the most recent years. Our inclusion and exclusion criteria to identify the literature of most relevance are described below.

Included in the REA:

Meeting all of the following criteria:

- Systematic reviews of outcomes related to generic treatments of cancer (the outcome is not pre-determined but resulting from the research)
- Qualitative analysis from focus groups, interviews or surveys about what is important for cancer patients
- Papers in English
- Research from or about any country
- Systematic reviews/REAs
- Papers published between January 2013 and January 2018.

Excluded from the REA:

- Outcomes related to non-medical interventions (e.g. the effect of physical exercise on the quality of life of patients)
- Outcomes not related to a drug treatment (e.g. surgical procedure, active surveillance, location of care, rehabilitation)
- Outcomes possibly related to interventions but with a long time span (e.g. well-being measures in adults who were cancer survivors when children)
- Outcomes that were pre-determined in the paper, i.e., established as an input rather than an output of the research (e.g. effect of treatment X on depression using the EORTC QLQ-C30 questionnaire)
- Papers in languages other than English
- Commentaries, editorials and features
- Papers published before January 2013.

Search strategy

The research topic has been split into three sub-areas: clinical outcomes, PROs and PREs. The latter sub-area has also been split into two dimensions: patient reported experience measures (PREMs) and general patient experience. Different search strategies were used in each area. Documents retrieved in the search for patient reported measures (PROs and PREs) were analysed together but separately from the documents identified in the search for clinical outcomes (which are rather different in nature from patient reported measures).

Clinical outcomes

Our objective is to identify any clinical outcomes recommended for, or used in, cancer clinical trials that are not solely for one particular type of cancer (in other words the outcomes are 'pan-cancer').

Note that our concept of 'clinical outcome' is not the same as the concept of "Clinical Outcome Assessment" suggested by a Report of the ISPOR Clinical Outcomes Assessment – Emerging Good Practices for Outcomes Research Task Force. That concept is too broad (encompassing Clinician Reported Outcomes, Patient Reported Outcomes, Observer Reported Outcomes and Performance Outcomes), with only biomarker outcomes not being embraced by it. Therefore it was decided to use a narrower interpretation.[42]

Databases:

[a] Search for lists of clinical outcomes or guidance documents produced by the European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), European Federation of Pharmaceutical Industries and Associations (EFPIA), International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), ISPOR, NICE, National Centre for Health Outcomes Development at the University of Oxford (NCHOD);

[b] Search for clinical outcome requirements and guidance in European Medicines Agency (EMA), and the Food and Drug Administration (FDA);

[c] Additional search of already known papers and citations in: CONCORD-3,[43] Liang et al.,[44] Fiteni et al.,[45] Herzog et al.,[46] Chakraborty,[47] Kemp and Prasad,[48] Morrell et al.[49] Luckett and King,[50] and Mott.[51]

Limits applied: for [a] and [b], the most recent list/guidance was reviewed.

Patient reported outcomes (health-related)

Databases: PubMed

Search terms in abstracts and titles.

The following search terms were used to search the above databases. Papers were included that contained any one of the terms in parts A and any one of the terms in part B and any one of the terms in part C: AND/A-C

<u>(A). Search terms for drugs:</u>

1. medicine(s)
2. pharmaceutical(s)
3. drug(s)
4. episode(s)
5. treatment
6. technology
7. OR/1-6

<u>(B). Search terms for cancer:</u>

1. cancer*
2. neoplasm*
3. tumor(s)
4. tumour(s)
5. carcinoma
6. oncolog*

7. OR/1-6

(C). Search terms for health-related quality of life patient reported outcomes:

1. “quality of life” OR QOL OR HRQoL OR “health status” OR “patient-reported” OR “patient reported”

2. scale(s) OR outcome(s) OR measure* OR instrument(s) OR questionnaire(s) OR dimension(s) OR domain(s)

3. patient(s)

4. AND/1-3

Patient reported outcomes (experience) -PREMs

Databases: PubMed

Search terms in abstracts and titles

Parts A and B are searched in combination with C: AND/A-C

(A). Search terms for drugs/outcomes:

1. medicine(s)
2. pharmaceutical(s)
3. drug(s)
4. episode(s)
5. treatment
6. technology
7. outcome(s)
8. OR/1-7

(B). Search terms for cancer:

1. cancer*
2. neoplasm*
3. tumor(s)
4. tumour(s)
5. carcinoma
6. oncolog*
7. OR/1-6

(C). Search terms for patient reported experience measures:

1. measure(s) OR measurement OR measuring OR measured

2. “patient-reported experience(s)" OR “patient reported experience(s)" OR “patient self-reported experience(s)" OR “PREM(s)” OR "patient experience(s)" OR "patient-experience"

3. AND/1-2

Patient reported outcomes (experience)- general

Databases: PubMed

Search terms in abstracts and titles

Parts A and B are searched in combination with C: AND/A-C

(A). Search terms for drugs:

1. medicine(s)
2. pharmaceutical(s)
3. drug(s)
4. episode(s)
5. treatment
6. technology
7. OR/1-6

(B). Search terms for cancer:

1. cancer*
2. neoplasm*
3. tumor(s)
4. tumour(s)
5. carcinoma
6. oncolog*
7. OR/1-6

(C). Search terms for patient reported experience outcome measures:

1. patient(s)

2. outcome(s) OR measur*

3. “matters to patients” OR “matters to a patient” OR “important for patients” OR “important for a patient” OR “important to patients” OR “important to a patient” OR well-being OR wellbeing OR “patient's experience” OR “patients' experience” OR “patient's experiences” OR “patients' experiences” OR happiness OR happy OR “patient's priority” OR “patients' priority” OR “patient's priorities” OR “patients' priorities” OR “priority for patients” OR “priority to patients” OR “patient perspective” OR “patient's perspective” OR “patients' perspective” OR “patient needs” OR “patient's needs” OR “patients' needs” OR “patient wishes” OR “patient's wishes” OR “patients' wishes”

4. AND/1-3

We pooled the results related to all patient reported outcomes (health-related, experience - PREMs and experience-general), to which were added six further references from the grey literature. Additional literature was identified in discussion with the Steering Group, as well as through discussions with experts in the field.

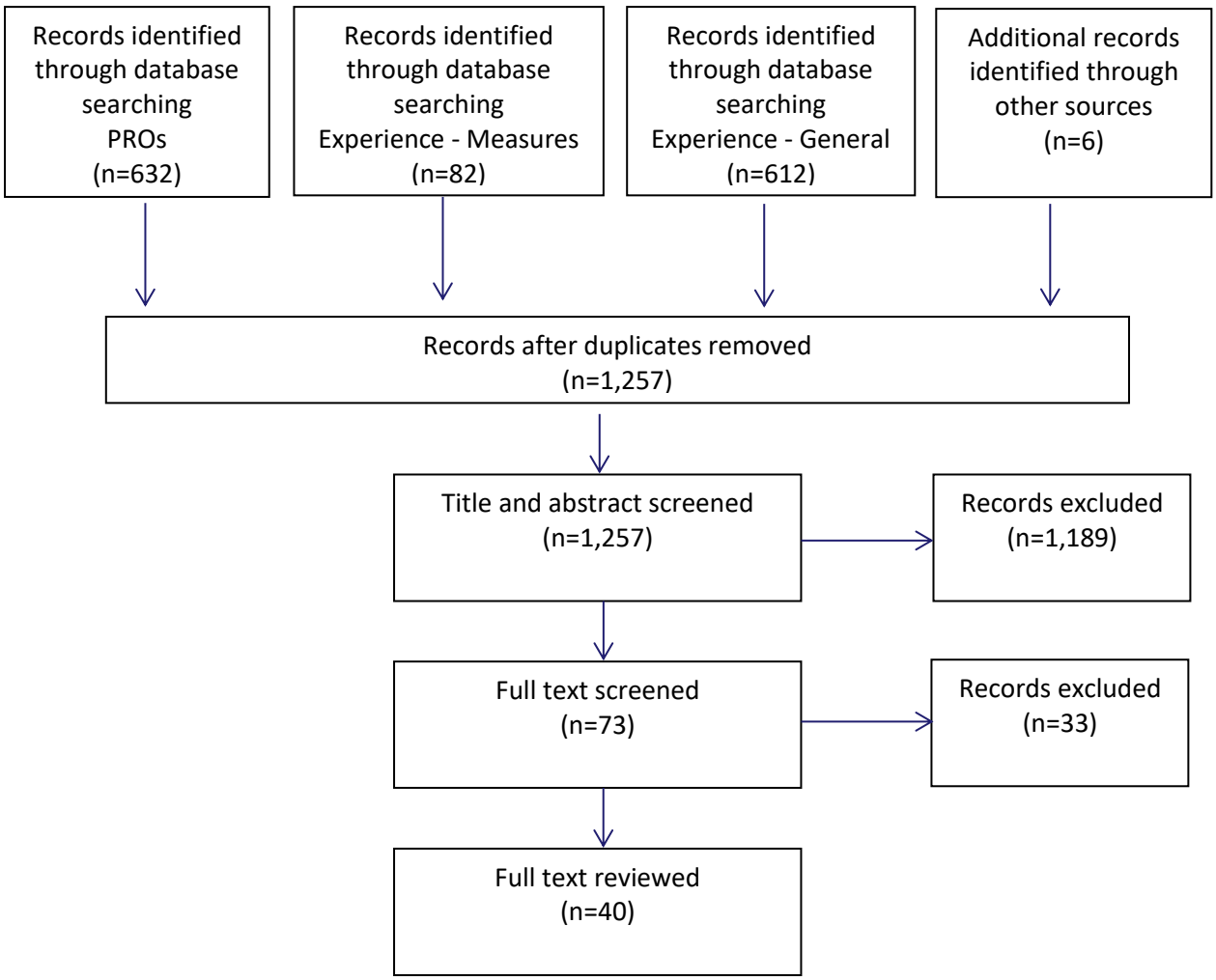
Search outputs

The guidance documents reviewed in the first search ('Clinical outcomes' [a] and [b]) did not offer any detailed lists of recommended clinical outcomes across all cancer sites/types. More information could be retrieved if searching for particular cancers. From search [c] a list of the most frequently recommended clinical outcomes was built to be included in randomised controlled trials. Some examples are provided below.

Figure 4 provides a graphical representation of the literature identified in the search focusing on patient reported outcomes and patient reported experience, as well as the results of each stage of the sifting process. Titles, abstracts and full texts were reviewed by two researchers (PCM and AC). A random sample of 50 papers were screened by both researchers to ensure the inclusion/exclusion criteria were applied consistently.

A total of 1,332 individual records were identified in the initial search. Removing duplicates left 1,257 unique papers. The title and abstract of each paper were then scanned to exclude articles outside the scope of the review, and the result was that 73 potentially relevant articles were selected. After full text screening, 33 papers were excluded, one of which was excluded because access to the full text could not be obtained. This left 40 papers for full text review.

Figure 4: Patient Reported Outcomes (PROs) and Patient Reported Experience (PRE): PRISMA Flow Diagram



Data extraction

Data extraction from all papers was done by one of the researchers who had previously reviewed the full texts (PCM). Where available, information was extracted into a standardised template on the following items:

- Methodology: quantitative/qualitative, systematic literature review, survey, interview, focus group, other
- Cancer site
- Sample size
- Cancer treatment
- PROM/PREM - data collection method
- Discussion of relative importance of measures included (by author)

Findings

Summary of the literature review

From the papers obtained from the first part of the search (clinical outcomes), a list of the most common clinical outcomes used across the different cancers was created.

None of the clinical outcomes or guidance documents reviewed here provided a comprehensive list of recommended endpoints for all cancer types. For instance, the published Consolidated Standards of Reporting Trials (CONSORT) best-practice guidelines does not present a list of preferred clinical outcomes, but encourages the reporting of "clearly defined primary and secondary outcome measures".[45] The choice of endpoints in cancer trials is considered as a major issue in the papers examined. For instance, Liang et al.[44] identify all the clinical endpoints used in every phase III cancer RCT published between 2013 and 2015 in five top journals of the area (345 papers). The authors report that 94% of the RCTs use time-to-event primary endpoints (with overall survival set as a primary endpoint in 36% of the trials), followed by response rate (5%) and toxicity or symptom scale (11%). The authors also noted that some studies used multiple types of primary endpoints.

The references reviewed from the second part of the search (see Figure 4) show a wide variety of interpretations for the meaning of the concept 'outcome', as well as a lack of consistency in the nomenclature: the term 'outcomes' is frequently alternated with 'items', 'aspects', and 'measures'. The concept of 'patient-reported experience' is also frequently used with little consistency across papers. This confusion is partly created by the NHS definition of PREMs, which relates patient experience to health care, rather than focusing on experience with treatment. In several of the papers reviewed, PRE is ultimately interpreted as patient experience with their last visit to hospital (see for instance the *Outcomes and Experiences Questionnaire*).[52]

Figure 5 and Figure 6 below illustrate the taxonomy developed by the reviewers to structure the analysis of the different 'outcomes' and 'outcome measures' identified.

Figure 5: A framework to classify 'Outcomes'

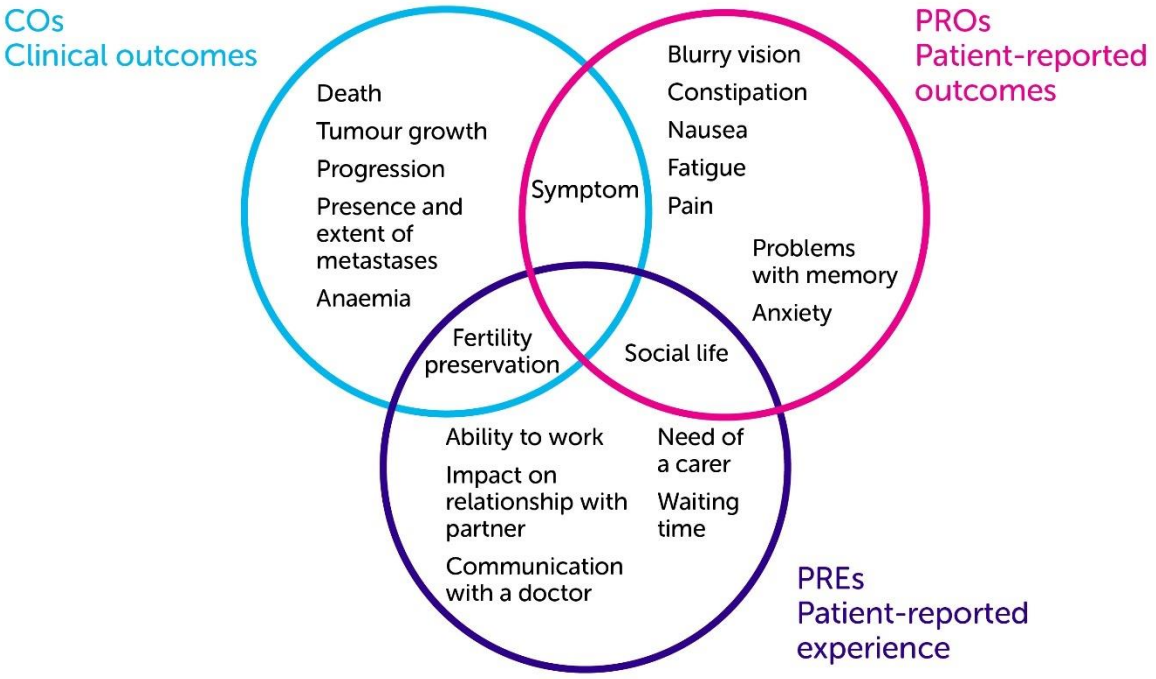
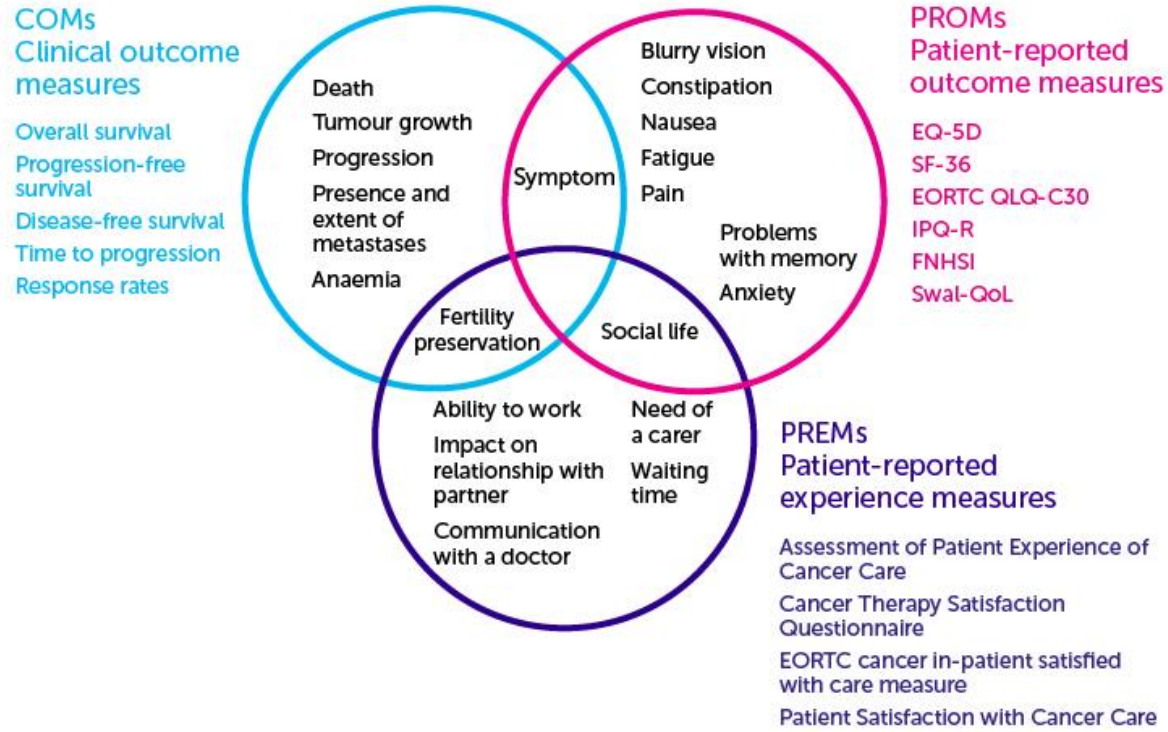


Figure 6: A framework to classify 'Outcome Measures'



Results of the literature review

The most frequently recommended clinical outcomes to be included in randomised controlled trials across the different cancers are listed below (in no particular order):

- Overall survival
- Progression-free survival
- Disease-free survival
- Tumour response (Response evaluation criteria in solid tumors or RECIST)
- Time to event (excluding overall survival)
- Time to progression
- Time to tumour growth
- Objective response rate; e.g. RECIST, radiological tests or physical examinations
- Response rates (complete, partial, stable disease, progressive disease)
- Toxicity or symptom scale

Overall survival was the only clinical outcome considered in all the documents reviewed.

For the second part of the analysis, the reviewed papers were grouped into four categories, according to the content of the paper. The classification of outcomes into the PRO and PRE groups is based on two main characteristics: who reports the outcome, and whether it is health-related or not. This definition is also used in several of the reviewed papers.[38 40] The groups are listed in Table 5 below.

Table 5: Number of references in each group of literature

Group	Definition	No. references
Group 1	Adults (18+) Patient reported outcomes (PRO)	17
Group 2	Adults (18+) Patient reported experience (PRE)	11
Group 3	Adults (18+) Core Outcome Sets	9
Group 4	Adolescences and young adults (approx. 14-24)	3

The papers captured in these groups are summarised below. We do not list all of the outcome or experience measures that are described in each paper, but where available we summarise any discussion of the relative merits of the measures (i.e. discussions of preferences or rankings of measures), as described in the literature.

Group 1: Adults (18+) Patient reported outcomes (PRO)

Literature in this group corresponds to papers describing a systematic review of all the existing PROs related to a particular scenario. These literature reviews are generally aimed at informing subsequent analysis in research projects. Papers usually review publications from randomised controlled trials, and they are linked to a cancer site: bladder,[53] brain tumours,[54] breast,[55 56] head and neck,[57 58] neuroendocrine tumours,[59] oesophageal,[60] ovarian,[61 62] prostate,[53 63 64] and skin.[65 66] Two papers which review the validity of all PROMs adapted to cancer patients were the exception.[67 68]

Of interest is the different search criteria used in the 17 systematic literature reviews to identify what was commonly addressed as 'outcome' in every paper. The terms 'adverse events', 'efficacy', 'endpoints', 'HRQoL', 'patient's experience', 'patient's satisfaction', 'psychosocial outcomes', 'side effects', 'symptoms' and 'toxicity' appeared in different searches, this shows how broad the scope of the concept 'outcome' is.

Only two papers explore the existence of rankings or preferences over outcomes or outcome measures. In the context of ovarian cancer, Ahmed-Lecheheb and Joly [61] remark that the greatest problems among the patients needing attention and action are: physical and psychological symptoms, treatment sequelae, and sexual problems. For skin cancer, Lee et al.[66] conclude that the Skin Cancer Index (a condition-specific measure) demonstrates the greatest evidence of its usefulness in patients with basal or squamous cell skin cancer.

Group 2: Adults (18+) Patient reported experience (PRE)

This group of papers encompasses the literature that explores which aspects of health care and health care outcomes are important for patients, usually from the patients' viewpoint. About half of the papers derive their information from focus groups,[40 69] interviews or surveys of patients,[39 70-72] and the views of caregivers and clinicians are also captured.[73] In these papers, patients are asked to rank items/dimensions/symptoms by their importance, and therefore preferences for different outcomes or outcome measures are derived. The remaining papers derive their results from systematic[74-76] or non-systematic reviews.[40 77]

The search criteria used in the different papers is more homogeneous than in the first group: the most frequently used keywords are: 'patient experience with cancer';[70 71 73] 'patient experience with care';[73] 'patient needs';[75] 'patient preferences over outcomes';[39 40 69 74 76 77] and 'patient satisfaction with outcomes'.[72]

All the papers reviewed provide information about rankings or preferences over outcomes or experiences. In open questions in surveys/focus groups, patients mentioned the following items about their *experience*: communication between patient and doctor,[73] effective clinical guidance throughout treatment,[69] waiting time during treatment and post-treatment phases,[73] staffing and resource levels,[73] speed and quality of diagnostic services,[73] and need for mental health support.[73 75]

A topic that appeared frequently in the papers was the ability to cope with the *symptoms* or *side effects* of medications. Hui et al.[71] classify the symptoms that cancer patients would prefer to control in three groups (from the most to the least important): [1] nausea; [2] depression, anxiety, drowsiness, well-being, dyspnoea (shortness of breath), sleep; and [3] pain, fatigue, and appetite. This is consistent with the findings in the specific area of lung cancer, where nausea and vomiting seem to be the most important side effects that patients wish to avoid.[76] For bowel cancer, Cranley et al.[77] find that, when considering treatment options, patients are less willing to tolerate more common side effects (such as nausea, fatigue or pain) compared to less likely but more clinically serious adverse events (such as heart attack or stroke).

In the discussion about preferences over *treatment outcomes,* six of the papers reviewed in this group show that most of the patients consider life extension to be more important than HRQoL or undesirable side effects.[39 40 69 74 76 78] Several papers provide a list or ranking of the most important outcomes for patients. For instance, in the context of head and neck cancer 'being cured' and 'surviving' are consistently ranked at the top of the list, followed by fear of recurrence, dental health, social function, pain, energy, swallowing, speech, chewing, voice, appearance, expenses for the treatment, and being treated closer to their home.[74]

In Minion et al.,[39] ovarian cancer patients are asked to rank eight treatment outcomes from most important to least important. The most important or desirable to the least are: cure, live longer but no cure, feel healthier, tumour shrinks, extending interval between chemo, reduce chemo-induced or cancer-induced symptoms, treatment cost. Most important outcomes for breast cancer patients are listed as: prognosis, survival rate, recurrence, adverse effects, and percentage cured.[40]

One paper[39] also collected ovarian cancer patient preferences across specific quality of life outcomes. Patients ranked the outcomes (from the most important or desirable to the least) as follows: feeling well; fewer interruptions to daily activities; less pain; less frequent hospital or doctor visits; less drug administrations; normal intimacy with partner, and low treatment cost.

Note that Fayanju et al.[40] is the only paper extracted and reviewed that shows a full description of value-based outcome metrics. The authors extract a list of outcomes from a systematic literature review, use focus groups to select the most important outcomes for breast cancer, and provide a full description of how these outcomes could be valued, and the full process through which value-based measures as well as dynamic capture of these metrics would be developed. For illustrative purposes, Table 6 reproduces the full description of one of the outcomes.

Table 6: Full description of value-based breast cancer outcome metric for "Return to normal activities of daily living"

Return to Normal Activities of Daily Living	
Description:	Percentage of patients who are able to return to baseline (i.e., pre-treatment) activity within 12 months of completing treatment for breast cancer
Time Points:	Baseline (pre-treatment); 1 year, 3 years, and 5 years after completion of treatment
Patient Population:	All newly diagnosed patients with Stage 0, I, II, III breast cancer
Numerator:	Patients who are able to return to activities of daily living 12 months post-treatment completion at level ≥ their baseline score
Denominator:	All patients who have completed treatment at MD Anderson
Inclusion Criteria:	N/A
Exclusion Criteria:	Patients who do not complete the FACT B+4 Survey at baseline and at 12 months post-treatment completion
Targets:	None
Data Stratification:	Age, Stage, Treatment Type (Chemo Regimen, Radiation Dose, Type of Surgery), Receipt and Type of Reconstruction, Adjuvant Hormonal Therapy
Purpose:	Collected for External Reporting, Internal Tracking, and Benchmarking
Data Source:	FACT B+4 Questions GF1-GF7
Miscellaneous Info:	None

Source: Reproduced from Fayanju et al.[40]

The results shown in Fayanju et al.[40] are useful, but with several caveats: first, the authors do not use a survey to support the main conclusions from the focus groups, and therefore the outcome selection criteria is supported by weak arguments. Second, Fayanju et al. seek to identify the most relevant health care outcomes, which overlap but do not totally fit in the scope of treatment-related outcomes, which is the purpose of the current report. In addition, the authors focus on breast-cancer and do not explore the potential generalisation of their core set. Finally, the value-based framework suggested in the paper is not designed in view of a future application as an OBP scheme, and therefore the feasibility of the scheme or implications of subjectivity in the patients' responses are not adressed.

The REA suggests that preferences are quite heterogeneous across the population, and particularly by cancer site. The analysis in Minion et al.[39] makes a good distinction of how patients value different symptoms, depending on the intention to treat. They compare participant's responses to what symptoms are considered unacceptable according to a scenario where therapy with a cure is possible, to one where there is recurrent therapy with an unlikely cure. Preferences are reported to vary by intention to treat. The work of Blanchard et al.[74] however shows that priorities seem relatively stable over time.

Group 3: Adults (18+) Core Outcome Sets

This group encompasses a set of papers that seek to define a set of core outcomes, that is, an agreed minimum set of outcomes or outcome measures that are considered to be essential for a particular cancer type. Most of the papers reviewed present the core outcome set as a recommendation of what should be measured and reported in all trials in the specific area. Two of the reviewed papers[36 37] suggest a list of outcomes that can be considered for a common algorithm across all cancers (listed in Table 7 below). The remaining papers focus on bladder,[79] head and neck,[80] oesophageal,[35] ovarian,[81] prostate,[34 38] and gastrointestinal (colorectal, liver, oesophageal, gastric).[82]

The methodology applied to define the core outcome set is similar across the reviewed papers. Almost all the papers undertake a systematic literature review of outcome measures (with the exception of Basch et al.,[37] which is a commentary of the core outcomes listed in Reeve et al.[36]). Notably the search criteria differ between papers: some papers only look at the core symptoms;[36] others look for core domains;[34 79] search for core outcomes;[35 38] or use both core symptoms and core domains for the search.[80 81] As well as utilising a literature review, one paper uses focus groups;[79] three use recommendations from a panel of stakeholders;[34 36 38] while one[38] also conduct semi-structured interviews with patients.

The wide range of PROMs used in trials, as well as the multiple scales, confusing terminology, and the inconsistent pooling of items and domains, were aspects frequently mentioned in the papers as a limitation of the analysis.[35] As a result, outcome sets are found that include 'items' such as 'urinary incontinence' and 'physical wellbeing', with the former pointing at a very specific symptom, and the latter describing an abstract wellbeing construct.[34]

Table 7 provides a description of the sets of core outcomes/domains/symptoms suggested in each paper. Note that elements of the sets are often defined by subgroups. For instance, defining of different core set of domains for localized and for advanced prostate cancer;[34] differentiating between core outcomes that apply to all interventions, and those which are intervention-specific,[38] referring to a list of 32 outcomes classified into generic and condition-specific.[35]

Table 7: Sets of core outcomes

Reference	Concept	Cancer	Items
Reeve et al.,[36] Basch et al.[37]	Symptoms	All	fatigue, insomnia, pain, anorexia, dyspnea, cognitive problems (includes memory or concentration impairment), anxiety (includes worry), nausea, depression, sensory neuropathy, constipation, diarrhea
Chen et al.[34]	Domains	Prostate	**For localised cancer**: urinary incontinence, urinary obstruction and irritation, bowel-related symptoms, sexual dysfunction, hormonal symptoms. **For advanced cancer**: pain, fatigue, mental well-being, and physical well-being
MacLennan et al.[38]	Outcomes	Prostate	survival (death from prostate cancer, death from any cause, local disease recurrence, distant disease recurrence/metastases, disease progression, need for salvage therapy); bowel function (bowel function, faecal incontinence); urinary function (stress incontinence, urinary function); sexual function; quality of life
Chera et al.[80]	Symptoms Domains	Head & Neck	**Symptoms:** swallowing, oral pain, skin changes, dry mouth, dental health, opening mouth/trismus, taste, excess/thick mucous/saliva, shoulder disability/motion, voice/hoarseness. **Domains**: social, functional
Donovan et al.[81]	Symptoms Domains	Ovarian	**Symptoms**: abdominal pain, bloating, cramping, fear of recurrence/disease progression, indigestion, sexual dysfunction, vomiting, weight gain, weight loss. **Domains**: physical, emotional
Perlis et al.[79]	Domains	Bladder	**Cancer-specific:** urinary, sexual, bowel, body image. **Generic**: pain, vigour, social, psychological, sleep, functional, family relationship, medical care relationship
Macelfield et al.[35]	Domains	Oesophageal	**Generic**: emotional function, role physical/activities of daily life, physical function, social function, generic health, sleep, global quality of life, cognition, role emotional, financial issues, spiritual issues
Pullmer et al.[82]	Symptoms	colorectal, liver, oesophageal, gastric	bowel-related, pain, eating-/taste-related, trouble for digestion, fatigue, physical appearance, deglutition, dysphagia, itching, nausea, weight loss

Table 7 shows variability in core outcomes by cancer site. For example, social and functional domains are selected as the core outcomes for head and neck cancer,[80] whereas the core domains for ovarian cancer are physical and emotional.[81] Additionally, even papers that address a similar cancer report different core outcomes.[34 38]

The degree of functionality of the core outcome sets suggested by the authors varies across papers. Perlis et al.[79] list 169 items extracted from a systematic literature review, classify these into 12 domains, and then select the 83 most important items (through focus groups) to define the list of core outcomes for bladder cancer. The high number of items is a limitation of the paper. Macefield et al.[35] examine 21 PROMs related to oesophageal cancer, extract 94 verbatim scales/items (such as pain or physical function), to posteriorly create 32 conceptual generic or symptom-specific domains. The authors claim that their core domain set will be useful as a framework to identify the core items (within domain), but the list of domains is large, which will likely diminish the application and impact of their core set.

Group 4: Adolescents and young adults (approx. 14-24)

In this group is included literature targeting only adolescents and young adults, approximately in the age group of 14-24. The three papers classified in this group do not focus on a particular cancer site.

Furness et al.[83] quantitatively analyse the responses to UK cancer patients' experience surveys between 2010 and 2014. They found that 16-24 year-old patients consistently reported a poorer experience of cancer care across the majority of domains than patients aged 25 or above. This may in part be due to the subjectivity of experience, with older patients having more life experience. Nonetheless, younger patients reported longer waiting times before referral and diagnosis.

A systematic literature review in Sodergren et al.[84] considers adolescent and/or young adult-specific outcome measures, as well as existing measures that have been adapted for adolescents and young adults. They find that the most common cancer-related issues (by number of citing articles) are: fatigue, loss of strength, pain, cognitive difficulties, hair loss, impaired appetite and desire to eat; ability to engage in everyday activities, partaking in sports, attending school and interacting with others; and feeling disconnected and isolated from their peers. Comparatively these look similar to those identified in the core outcome set papers, although some issues will be age specific (e.g. everyday activities and schooling).

Johnston et al.[85] also undertake a systematic review of PROMs of peripheral neuropathy (a side effect of cancer treatment) in children, adolescents and young adults. No high-level list of outcomes nor the relative importance of measures or outcomes was provided.

Creating an outcomes framework

The information extracted from the reviewed papers was highly variable. There was a wide variety of outcomes used, with items pooled without a clear structure of dimensions, domains or categories to classify them. In an attempt to summarise and provide some insight on an outcomes framework that can be used in OBP schemes we first focussed on those papers which provided a list of outcomes organised in a clear structure, then considered the literature within this subset where outcomes were selected based on their relative importance (by focus groups, interviews, or systematic reviews, and from the perspective of patients, carers, government or industry).

Preference was given to papers classifying the items in a clear and well-structured framework. This resulted in a set of eleven papers.[35 36 38-40 58 59 64 66 79 84]

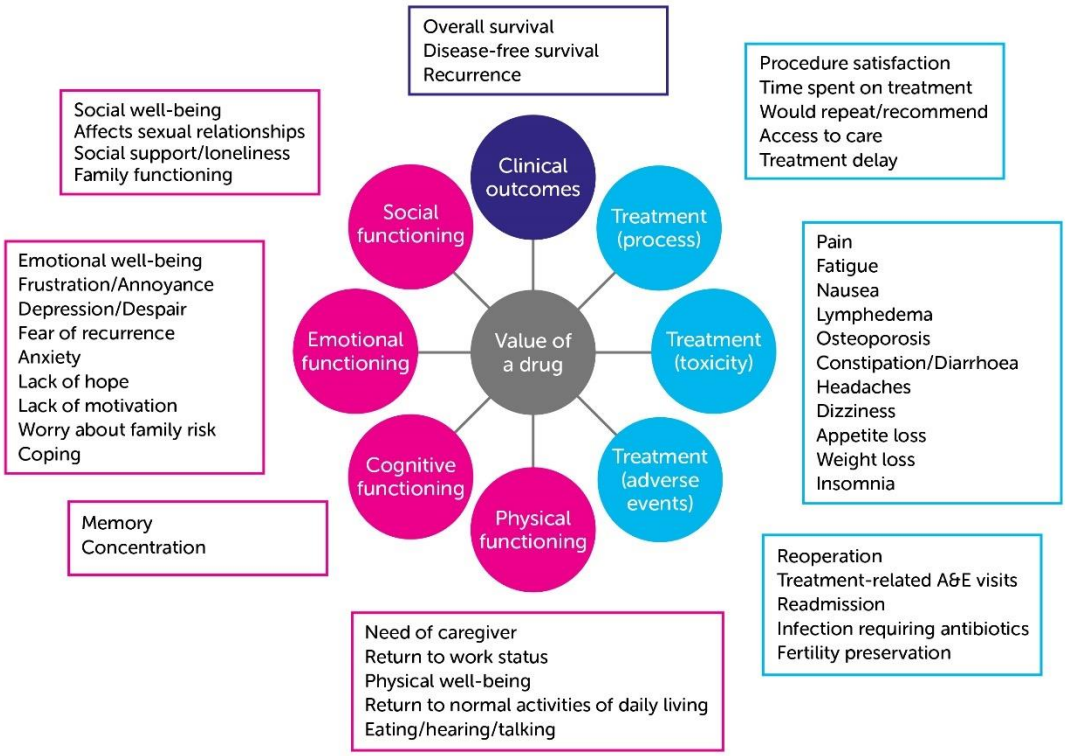
In a second step, given the classifications commonly used to define outcomes (not just in the oncology space but more generally), high-level domains of outcomes or *value elements* were created:

- Clinical outcomes
- Treatment (process)
- Treatment (adverse effects)
- Treatment (toxicity)
- Physical functioning
- Cognitive functioning
- Emotional functioning
- Social functioning

In a third step, the items/outcomes provided in the papers listed above were classified into one of our eight categories. This allowed validation of our outcomes framework (i.e. how well the different items fit into it), and also allowed us to identify which items were more frequently reported in the papers.

Following the current literature on value frameworks which uses a visual of a 'value flower',[86] an 'outcomes flower' was created, where the centre is the value of drug and the high-level domains are petals. Figure 7 presents the flower with a list of the most frequent items classified into each petal/element.

Figure 7: Outcomes Flower



As a final step, we went through the generic and cancer-specific measures that were listed on the papers reviewed, in order to identify the 'best' measure which could capture the petals (and most of the outcomes) shown in Figure 7. We could not find any outcome measure, PROM or PREM, that encompasses all the elements.

Conclusions

The literature review identified a general lack of consensus about the following aspects: the definition and interpretation of outcome, and distinction between 'outcome' and 'treatment outcome'; the definition and interpretation of 'patient experience' and 'patient outcome'; the distinction between 'outcome' and 'outcome measure'; the use of the terms 'item', 'symptom', 'outcome', 'aspect', 'dimension' and 'domain'; the use of a well-defined framework to classify the outcomes; and the identification of the gold standard methodology for determining the most important outcomes.

Many of the papers extracted were reviewing existing PROMs, pooling items in questionnaires, and seeking to put some order on these (e.g. grouping the items in different domains/dimensions and identifying the core ones). Reviewed collectively it is our opinion that they fail to achieve this objective. The methodology used in these papers involved qualitative analysis and subjective assessment, and therefore their findings have a lack of generalisability. Very few papers discussed the relative importance, or relative weights, attached to different measures.

In an attempt to establish a core outcomes framework that helps provide boundaries for outcomes that could be linked to price in an OBP scheme, an outcomes flower was created. The flower confirmed that no current instrument or questionnaire exists that covers all the elements of outcome. In some instances it may not be necessary to consider all the elements of the framework, for example patients may have strong preferences for some elements over others. This requires investigation and research to understand patients' willingness to trade the various outcomes of cancer treatment.

Appendix 3 – Interviews

Objective

The purpose of the interviews was to build on the findings of the two literature reviews by obtaining a range of perspectives on the practicalities of OBP schemes. The emphasis was on identifying the full spectrum of relevant views rather than to generate a single consensus position. Thus the interviews gathered informed views on:

- The desirability and practicality of linking the prices paid for medicines to the outcomes they achieve;
- The types of outcomes that are most meaningful to link to price, both in general and specifically for cancer medicines;
- The availability of data, currently or potentially in future, for measuring those outcomes;
- Enablers of, and barriers to, linking a medicine's price to measured outcomes; and
- Preferences, if any, between different options for the form of OBP.

Method

Thirteen interviews with key informants were undertaken: NHS cancer clinicians; commissioners of cancer services and collectors of cancer data, including NHS England and PHE; pharmaceutical companies with pipelines of new cancer medicines; and international academic experts on OBP. (Separate discussions with patients were held in two focus groups, which are described in Appendix 4.) Potential interviewees were identified by the members of the project Steering Group and by the research team based on key authors identified from the literature reviews.

The interviews took place between mid-May and early July 2018. Explicit consent was obtained for all interviews. Interview duration was between 30-60 minutes in each case. Interviews were semi-structured to permit comparability of findings across interviewees, combined with some freedom to allow interviewees to raise and develop themes of particular concern. The interview topic guide is reproduced in the Annex to this Appendix. Each interview was conducted by a member of the research team (AC, PC-M, JP, JS). Interviews were audio recorded with the interviewees' consent, which was given in every case, to aid subsequent analysis.

In each case the interviewer noted the main points raised by the interviewee, referring to the audio recording as necessary, and shared the written notes with all other members of the research team. The notes were reviewed by all members of the research team and were then discussed at a research team workshop to extract common themes and the range of views offered within each theme, according to the interviewees' different perspectives. These themes and the range of views obtained are described in the following pages.

The interview stage was reviewed by and received ethical approval from the Biomedical and Health Sciences, Dentistry, Medicine and Natural and Mathematical Sciences Research Ethics Subcommittees (BDM RESC) at King's College London, Ref: LRS-17/18-5723.

Findings

The limited number of interviews, 13, covering a range of stakeholder groups, means that analysis of them is qualitative. What matters is the information imparted from each perspective rather than the number of occasions that a particular point was made in the 13 interviews. The interview findings have been grouped into eight major themes, all of which concern two or more of the five areas of questioning that were listed under the objectives above. The themes are:

1. Objectivity of outcome measures
2. Context specificity of outcome measures
3. Linking the outcomes observed to the medicine used
4. The simplicity of the OBP scheme
5. Timescale for measuring outcomes and adjusting prices
6. Data
7. Institutional constraints
8. Responsibility and stakeholder will to make an OBP scheme work

The following paragraphs consider each theme in turn. They are followed by a concluding section which draws together what was learned overall from the interviews in terms of the objectives.

Objectivity of outcome measures

Given the potentially major financial implications to both the NHS and the manufacturers of the medicines whose prices might be linked to outcomes, it is unsurprising that a strong theme to emerge from the interviews was the desire by all stakeholders for the outcomes measure(s) used to be objective. In other words, it should not be possible for any party to 'game' the level of the outcome that is recorded:

> *"If outcomes are not objective then the system can be gamed."* (Academic)

and the meaning of the outcome measure must be clear:

> *"The more subjective the outcome the more difficult it is to capture."* (Government)

Outcomes such as progression-free survival are clearly objective measures. There was consensus that quality of life was also an important area of outcomes to take into consideration. But there were differences of view about the objectivity of patient reported outcome measures (PROMs):

> *"PROMs might be used in future but some dislike them as too subjective."* (Academic)

A clinician noted also that:

> *"It is important to incorporate carers' feedback, since they are the ones who can add relevant information related to the practicalities of the treatment."* (Clinician)

An industry interviewee also expressed wariness about the possible subjectivity of some outcome measures. However there are well-validated PROMs available, both cancer-specific and generic (applying across all disease areas), that are already robust enough to satisfy HTA bodies when making reimbursement decisions and it should be possible to develop more specific PROMs in future if desired.

Context specificity of outcome measures

Cancer is not a single disease. A view heard in several of the interviewees is that the most relevant outcome measures for a cancer medicine will depend on the particular cancer being treated, its site and the stage it has reached at the time the patient is receiving treatment:

> *"You need to consider cancer type, solid tumours versus haematological malignancies."* (Industry)

"If payments are based on response rates, this might be ok for adjuvant patients, but if disease is metastatic then relevant outcomes will be very different [e.g. survival]". (Clinician)

> *"Selecting outcomes that will be generic enough to cover all cancers will be a challenge."* (Commissioner)

Clinical trials of the medicine concerned will have collected data on cancer-specific clinical outcomes and possibly also cancer-specific or generic PROMs. These could be a starting point for selecting the relevant outcome measures for any specific medicine:

> *"Start from the outcome measures collected in clinical trials."* (Industry)

Linking the outcomes to the medicine

For OBP to be feasible, the outcomes to be linked to price must clearly be ones that are expected to be affected by the medicine. But the medicine may be one of a number of factors affecting those outcomes. This raises the question of the comparator used in a real-world setting to determine the extent of outcomes attributable to treatment with the medicine:

> *"When using real-world data there is no control/comparator arm. There needs to be good historical datasets to compare real-world data with and draw conclusions, but such information may not exist."* (Academic)

A solution to the comparator problem was suggested by an interviewee from industry:

> "*Outcomes could be compared to the median value from clinical [trial] data, with the price regularly adjusted based on the difference between the real-world and clinical [trial] data"* (Industry)

However our attention was drawn by another interviewee to an OBP scheme in Australia for a medicine to treat pulmonary artery hypertension, where in the view of the interviewee:

> *"A causal link could not be inferred between the medicine and the outcomes measured, due to casemix"* (Academic)

In other words, the observed outcomes were for a different mix of patients from that of the population who were treated in the clinical trials of the medicine, so it was difficult to agree how much of the difference from expected outcomes was due to the different casemix rather than the performance of the medicine. The extent to which the real-world casemix is likely to differ from that for which there is existing evidence from trials, is therefore an important consideration when assessing the desirability of an OBP scheme.

Simplicity of the OBP scheme

Several interviewees considered that any OBP scheme should be kept simple in order to be practical. The default alternative pricing approach, which applies to the vast majority of medicines used by the NHS currently, namely a price per unit of medicine purchased, is very simple to operate. Price discounts related to the quantity purchased are barely more complicated and are also common. Consequently, only a simple to operate outcome-based

scheme will be seen by buyers and sellers of medicines as preferable to the non-outcome-based alternative:

> *"From experience, companies begin the process with good intentions to implement novel pricing arrangements, but generally end up falling back on a simple discount when the practicalities and implications are fully thought-through."* (Clinician/commissioner)

> *"We need to make outcome-based pricing schemes as simple as possible if we are to overcome the barriers."* (Academic)

The issue of simplicity came into particular focus when the interviewees were asked what they thought about whether price should be determined in a binary fashion: one price if the medicine achieves sufficiently positive responses, a lower (or zero) price if it does not; or with multiple price steps for different levels of response. While stepped schemes were attractive to a government interviewee, they were less so from an industry perspective:

> *"Agreements of a binary nature are easier to define. A full continuum would not be practical, but ideally a stepped approach would seem optimal."* (Government)

> *"Binary, all or nothing, price agreements are the easiest to implement. That is, the pharmaceutical company reimburses the NHS the full cost of a patient's treatment if certain criteria are not met. Stepped pricing would be administratively more costly."* (Industry)

Timescale for measuring outcomes and adjusting prices

The time at which outcomes are measured – how long after the treatment started or finished – may significantly affect the magnitudes of those outcomes and hence affect the price paid within an OBP scheme. This is particularly the case if price is determined patient by patient (e.g. one price if the patient responds to the medicine; a lower or zero price if they do not respond sufficiently):

> *"If quality of life data are collected to inform price on an individual basis, the time points for data collection (whether during treatment, shortly after, or post recovery) become very important and will have a huge impact."* (Clinician/commissioner)

This implies that an OBP scheme might need to specify when outcomes are to be measured.

Many outcomes require a significant passage of time before they can be known. That is obviously the case for the duration of survival or for the quality of life experienced over the remaining life course post-treatment. Waiting until outcomes are known, or merely able to be better estimated, implies a lag between the purchase of the medicine and the final determination of its outcome-based price.

Thus OBP introduces uncertainty as to the ultimate size of the payment that will be made by the NHS purchaser to the company supplying the medicine. NHS financial regulations make that uncertainty awkward to deal with in practical terms:

> *"Ideally the outcomes on which to optimally base price would be long-term clinical endpoints. But government accounting rules and NHS England funding cycles makes this impossible. Even two to four years would not be realistic. Therefore this timeframe element needs to be an important consideration in the outcome of choice, on top of what is clinically most relevant."* (Government)

> *"There would be complications around time lags for the outcome of interest. It is easy to work in a system where payment is made upon prescription. If payment is delayed until such a point that an outcome is achieved (or not), that would add huge uncertainty."* (Commissioner)

One interviewee pointed out the time lags that will inevitably exist between an outcome being measured and those data becoming available:

> *"There is a need to consider how 'live' data capture to inform payments needs to be. SACT [Systemic Anti-Cancer Therapy database] reports are generated monthly* [by hospital trusts and sent to SACT]*, but for full cancer registration data there is a much more significant lag. Consideration of timeliness needs to take into account the type of outcome upon which payments are being based."* (Government)

Data

The challenges presented by collecting outcomes data to enable OBP were mentioned in all the interviews. But perceptions of the ability of the NHS to collect and manage outcome data differed. One interviewee neatly summarised the issue:

> *"Anything is measurable given sufficient resource. The difficulty is in managing how and who collects the data, and ensuring there is sufficient resource to support."* (Clinician)

In other words there needs to be a data infrastructure and staff with sufficient time to populate it with outcomes data, and to ensure that the data are high quality and reliable (e.g. minimising missing and incorrect data).

Two of the three industry interviewees took the view:

> *"The lack of [data] infrastructure in the NHS is an issue"* (Industry)

> *"A strong data infrastructure is required, tracking patients across their NHS interactions, recording the treatments received and their outcomes"* (Industry)

and:

> *"Collecting non-clinical outcomes … should be an aspiration to work towards for now, as the current infrastructure is not in place."* (Industry)

Other interviewees said:

> *"The infrastructure for data collection is there, but investment is required to improve quality"* (Clinician/commissioner)

> *"The infrastructure is there. The system for data collection at the individual patient level in England is very advanced, but further work is required to define the outcomes of interest."* (Government)

Even if the requisite data infrastructure exists, OBP is, in the short term at least, going to be constrained by the data that are already being collected:

> *"There is not the funding at present to invest in significant extra data collection."* (Government)

But a reason for cautious optimism in the case of cancer treatment data was offered by one industry interviewee:

> *"Outcome-based pricing is more of a reality in oncology than other areas, due to the data that is being collected at the moment, e.g. SACT."* (Industry)

The same interviewee also drew attention to the AIFA web-based tool in Italy which provides an off-the-shelf way of collecting and accessing registry data. Another industry interviewee suggested that if full compliance with data submission needs could be enforced then SACT could be a foundation for the data needed for OBP for cancer medicines.

Institutional constraints

In addition to any limitations imposed by the current data infrastructure, or weaknesses in it, in the NHS in England, a few interviewees mentioned obstacles to OBP resulting from current institutional arrangements governing HTA decisions and regulating medicines prices paid by the NHS. Such issues are in principle surmountable by way of changes to those institutional arrangements, but they are a source of discouragement to OBP schemes in the short term.

One interviewee highlighted that OBP needs to align with NICE's procedures:

> *"Outcome-based payment arrangements must be linked with the NICE appraisal, and the key things that governed differences in the outcomes and uncertainties in the economic model."* (Clinician/commissioner)

More generally, the interplay of NICE HTA, the new CDF arrangements and the regulation of branded medicine sales to the NHS would all have to be considered and worked within by an OBP scheme were it to be set up today:

> *"There are now a wider set of circumstances in which a medicine can access a complex confidential deal, but the process is still fairly restrictive … how commercial arrangements will work going forward is tied-up with the ongoing discussions around the new PPRS [Pharmaceutical Price Regulation Scheme]."* (Government)

Value Added Tax (VAT) rules create their own complication:

> *"VAT must be paid for any drug that is dispensed within a hospital … Supposing an outcome-based scheme involves payment up front and a rebate for non-responders, the NHS will expect VAT to be included in the rebate from industry, as this is an outgoing that has had to be incurred and cannot be recouped from the Treasury. This actually makes a huge difference, and in practice has deterred many manufacturers … in order to avoid this extra monetary burden."* (Clinician/commissioner)

Responsibility and stakeholder will

A number of points made by a government interviewee noted that for OBP to work requires all stakeholders to take responsibility for enabling it to happen: industry, clinicians, NHS providers and commissioners, Government and patients. The same point was reflected by an industry interviewee who identified the need for a sharing of risk and effort between the NHS and the company selling the medicine.

If one or more stakeholders lack the will to make it succeed, OBP schemes will not happen. This includes patients, as data about the outcomes they experience when they take medicines is at the heart of OBP:

"It is therefore our responsibility to find a way – which is sustainable and affordable – of bringing promising therapies forward." (Government)

"All stakeholders must be on board, especially the patients." (Government)

"Patients must be convinced of the benefit, as data collection must meet the requirements of the GDPR and is likely to require explicit consent." (Government)

"The greater the number of external variables in play, the greater the sharing of the risk there should be. That is industry should not take all/majority of the risk." (Industry)

"[OBP] would require partnerships across national bodies, industry and patients. It should be completely transparent and based on fully-consented partnerships." (Government)

Taken as a whole, the interviews revealed either considerable support for, or at worst equanimity towards, the principle of OBP, while identifying a number of important operational challenges that need to be resolved in practice and which argue for keeping OBP schemes simple and data demands modest.

"Don't ask whether outcome-based pricing should be done; ask how it can be done." (Industry)

"Outcome-based payments for cancer drugs would be beneficial for society" (Clinician)

"Outcome-based pricing should be the future of pricing schemes for medicine where there is significant uncertainty about outcomes" (Industry)

"Everyone [industry and NHS] appears to be coming into alignment on the desirability of these deals, and how to make them work … Whilst there are operational concerns, the main parties are not unaligned in thoughts on outcome-based arrangements" (Government)

Summary

The information provided by the interviewees covers a broad range of perspectives and suggests the following overall findings in terms of the questions they were asked.

The desirability and practicality of linking the prices paid for medicines to the outcomes they achieve. The general impression gained from the interviews is that OBP is considered to be desirable where there is significant uncertainty about the outcomes that medicines will achieve in practice. But there is less consensus about its practicality.

The types of outcomes most meaningful to link to price. The interviewees expected these to vary according to the specific cancer medicine, the cancer being treated, its site and stage. The importance of quality of life outcomes is widely supported, in addition to survival. The desire for objective measures suggests that schemes will need to rely on well-validated measures when patient-reported outcomes are included.

The availability of data, currently or potentially in future, for measuring those outcomes. Interviewees all recognised the need for data infrastructure in the NHS, but differed in their view of how far such an infrastructure exists and is being used. There was rather more agreement that data collection, sharing and analysis require staff time that is in short supply, emphasising the importance of not imposing significant new data collection demands.

Enablers of, and barriers to, linking a medicine's price to measured outcomes. The main enabler appears to be shared recognition by patients, clinicians, NHS and industry of the potential importance of OBP in enabling access to new cancer medicines. Barriers concerned operational constraints, principally shortage of resources to collect additional outcomes data and institutional factors and financial/fiscal rules which are in principle surmountable but require changes to current arrangements.

Preferences, if any, between different options for the form of OBP. Taken together, the interviewees' responses did not converge on any particular preferred type of scheme, other than that it should be simple and based on objective outcome measures that are clearly linked to use of the medicine.

Annex 3A – Interview Topic Guide

Introduction to OHE/RAND and scope of the study

Q1 Can you tell us about your current role and your experience, including relevant previous roles, in order for us to understand your background?

Q2 What is your experience of either outcomes and their measurement, and/or of medicine pricing/reimbursement schemes? I.e. have you negotiated schemes, written about them, researched outcomes …?

Q3 What, in general, do you think of the idea of explicitly basing prices on outcomes for medicines? What if any experience do you have of outcome-based pricing schemes? Are you aware of any new schemes of that type currently being considered?

Q4 From your knowledge and perspective, which outcomes are most meaningful to patients, and does that differ from those most meaningful or appropriate to link to reimbursement/price for cancer medicines?

We now want to ask your views on the practicality of outcome-based pricing, the factors that might make it more practical (enablers) or might prevent it in practice (barriers).

Q5 Are the outcomes you mention measurable in practice given the need for data? Are you aware of any existing data that could measure them? Do you have any ideas for how data to measure them might be collected in future?

- Are the data currently collected, or could they realistically be collected, on the outcomes you deem most important to cancer patients?
- NHS or other sources of data (electronic health records, registers etc.)?
- SACT data, National Cancer Patient Experience Survey, similar?
- Are any important outcomes not measurable in practice?

Q6 How feasible is it to link price to measured outcomes where data either are, or could in principle be, available?

- Any resource and/or organisational changes required to enable this?
- Willingness of patients to contribute with data?
- Investment in data collection?
- Acceptability by society including thoughts about equity/fairness?
- Any other barriers to outcome-based pricing beyond any so far mentioned?
- Any other enablers to outcome-based pricing beyond any so far mentioned?

Questions 7 and 8 [Optional, if time allows and fits with interviewee's expertise]– more detailed questions about the mechanisms of an outcome-based pricing system

Q7 (If not already covered in answers to earlier questions.) To the extent that outcome-based pricing of medicines may be possible, do you think:

- It should be on an individual patient basis (one price for the medicine for each patient who responds positively to treatment, a lower price for each patient who does not respond positively)? If so, should that be on a binary (response/non-response) basis or a multi-stepped basis (e.g. strong response/weak response/non-response)?

- That it should rather be on the basis of one price for all patients' use of the medicine? Or different prices for different sub-groups of patients?
- That the initial price should be low and only raised if claimed outcomes are achieved; or that the initial price should be high with a rebate if claimed outcomes are not achieved; or somewhere in between with price going up or down based on outcomes achieved?

Q8 Do you have any thoughts/advice about how the monetary value of measured outcomes might be established in practice? Where multiple outcomes are to be linked to the price of a medicine, do you have any thoughts about how to aggregate them for that purpose?

Q9 In summary, what are your thoughts about the practicality or otherwise of outcome-based pricing for cancer medicines?

May we contact you again during the rest of the research for the purposes of clarification of points made during the interview?

Thank you for your time and the valuable insights you have provided.

Appendix 4 – Focus Groups

Objective

Two focus groups were run, each having different objectives. The first focus group aimed to identify which high-level treatment outcomes identified in the literature review are of importance to cancer patients, particularly when considering their own cancer drug treatments. In this context, high-level outcomes refer to the overarching outcomes included in the 'treatment outcomes flower' shown in Figure 8 below.

Building on the high-level outcomes identified in the first focus group, the second focus group aimed to identify a more specific list of important treatment outcomes and among those which are the most important. This information was then used to determine the wording of a survey of cancer patients and their carers (see Appendix 5).

The remainder of this Appendix describes the approach of each focus group, the discussions that were undertaken, and the outcomes of those discussions. Both focus groups received ethical approval from the BDM RESC at King's College London, Ref: HR-17/18-5907.

Recruitment and participants

Two focus groups with cancer patients were run – a total of nine participants in all. Both focus groups were facilitated by PL, assisted by JP. The first focus group took place in central Manchester on the evening of 28th June 2018, with five participants in attendance. The second focus group took place in central London on the evening of 19th July 2018, with four participants attending.

Participants were identified via a dedicated Cancer Research UK webpage, through which cancer patients could declare their interest in participating directly to the research team. All of those who declared interest were invited to participate, and were provided with an honorarium of £30 and travel expenses up to £50.

Table 8: Participants profile

Focus group	Identification number	Gender	Age category	Cancer
Focus group 1 – Manchester	1	Male	70+	Lung
	2	Male	60-69	Prostate
	3	Female	20-29	Bone
	4	Female	60-69	Breast
	5	Female	60-69	Breast
Focus group 2 – London	6	Female	30-39	Melanoma
	7	Male	70+	Prostate
	8	Female	50-59	Ovarian
	9	Female	40-49	Breast

Table 8 above provides more detail on the characteristics of participants at each focus group. Overall, a mixture of ages and genders were represented across the two focus groups, with females being most represented. Participants also drew on experience from a wide breadth of cancers, while a number had also cared for their partners or parents with cancer.

Focus Group 1

Method

Prior to the first focus group, participants were informed of the purpose of the discussions and sent a copy of the 'outcomes flower', shown in Figure 8, with an accompanying explanation for each 'petal', shown in Table 9. The outcomes flower displays the high-level outcomes that can potentially be brought about by cancer drugs. (More specific outcomes lie under each of the eight relevant 'petals', which were discussed in the second focus group.)

The outcomes flower is a product of the outcomes literature review (see Appendix 2), where all of the identified specific outcomes were found to lie under any one of the eight 'petals'. During the first focus group participants were specifically asked which of the high-level outcomes shown in Figure 8 were most important to them, and whether any were missing. It was emphasised that we were interested in the outcomes of medicines they received, or were offered but declined, during their treatment for cancer.

Figure 8: Outcomes Flower (simple)

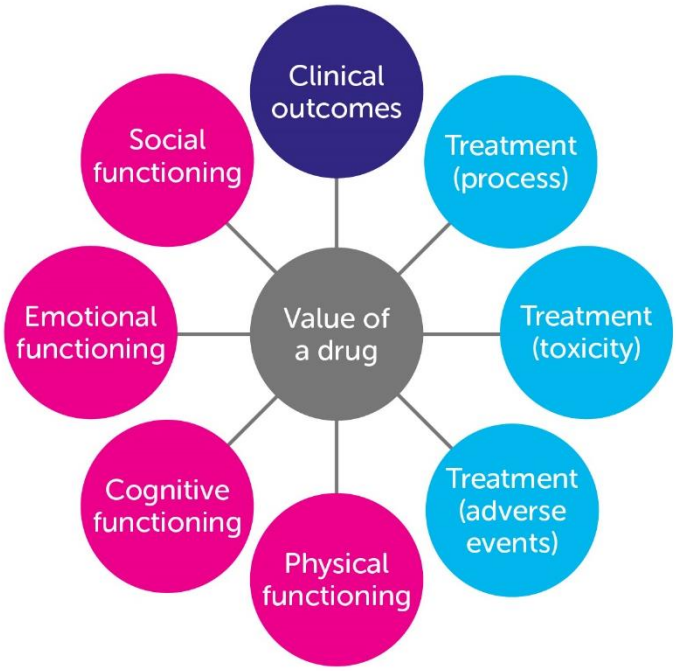


Table 9: Outcomes flower petal definitions

Petal	Definition
Clinical outcomes	Measurable changes in indicators of health as a result of a given treatment(s); *e.g. tumour growth*
Treatment (Process)	Outcomes related to the way in which treatment is provided; *e.g. time spent on treatment*
Treatment (Toxicity)	Outcomes related to the harmful clinical effects of a given treatment(s); *e.g. headaches*
Treatment (Adverse events)	Outcomes related to any untoward medical incident or event as a result of a given treatment(s); *e.g. treatment related A&E visits*
Physical functioning	Outcomes related to the ability of an individual to undertake basic and more complex activities; *e.g. return to work status*
Cognitive functioning	Outcomes related to the ability of an individual to undertake intellectual activity; *e.g. memory, concentration*
Emotional functioning	Outcomes related to the feelings of an individual; *e.g. anxiety*
Social functioning	Outcomes related to the ability of an individual to interact in everyday environments such as work, social activities, relationships etc.; *e.g. loneliness*

Views of Focus Group 1

Outcomes of importance

At one point or another throughout the discussion each of the petals was identified as important to at least one of the participants. However, it became clear that some outcomes were deemed more important than others. Clinical outcomes were regarded as the most important for participants, with a particular focus on life extension. Participant 5 was particularly concerned with life extension, stating "*how long I stay alive is the most important outcome for me*" [#5, female, breast cancer, 60-69], a point that she reiterated later in the discussion.

However, clinical outcomes were not exclusively of importance. Quality of life, as captured by the four "functioning" types of outcomes (Figure 8, pink petals), was also regarded as extremely important, if not as important as life extension. One participant argued that "*quality of life, not just length, is important*" [#2, male, prostate cancer, 60-69], with another saying that "*extending life is not the only outcome of importance, it is important to feel useful and that you are benefiting from being around*" [#4, female, breast cancer, 60-69] and another that "*it is important to have a sense of agency… [and] a feeling of getting back to normal"* [#2, male, prostate cancer, 60-69].

Treatment toxicity, in particular side effects, was also identified as an outcome of importance. Participant 1 spoke about his desire to spend time with his grandchild, which he would not be able to do had he undergone chemotherapy, because of the impact it would have had on his immune system as a treatment side effect. Another participant suggested that the potential side effect of infertility "*would be considerably more important for a younger person, particularly if they did not have any children yet*" [#4, female, breast cancer, 60-69].

Adverse events were also identified as important to participants, with a particular issue being raised around the potential need for reoperation.

The environment within which the drug is administered was also raised by participants, which comes under the treatment process heading in Figure 8, as some participants noted they would rather receive treatment in the comfort of their own home. However, others stated they enjoyed being able to socialise with other cancer patients while receiving treatment in a hospital setting (chemotherapy unit).

Finally, the impact of treatment and the wider cancer experience on family members was also identified as important, which sits under the social functioning heading. Participant 3 noted that this was particularly important to her as her family "*split for a while*" [#3, female, bone cancer, 20-29] following the cancer diagnosis.

Other areas of discussion

Separating the impact of the medicine from that of the wider cancer treatment

It is important to understand the context within which the focus group discussion was held when considering the outcomes that were deemed of importance. Although it was made clear that the discussion should focus specifically on the outcomes of cancer medicines participants had received, in reality participants struggled to separate their drug treatment experience from their wider cancer experience.

Because participants struggled to separate their drug treatment experience from their wider cancer experience, they also had difficulty separating the outcomes of their medicine from the outcomes of their continuum of cancer treatment (e.g. the diagnosis through to surgery through to radiotherapy and now the experience of 'living' with cancer). As a result of this, the outcomes of importance identified above should be seen as important across the whole cancer treatment experience, rather than specifically important to cancer drugs. This has implications for OBP schemes which rely on a clear causal link between treatment with the particular medicine and the outcomes observed.

Heterogeneity in outcomes of importance – context matters

All participants agreed that heterogeneity exists in the outcomes of importance depending on the characteristics of the individual in question, the cancer they are being treated for, the drug they are receiving, and other context specific factors. For example, participants agreed that the age of the patient would influence which outcomes were most important to them. They felt that clinical outcomes are relatively more important for older patients, whereas 'functioning' outcomes are relatively more important to younger patients.

Moreover, one participant stated that there are "*cultural nuances with respect to the preferences of different people when considering which outcomes are important*" [#4, female, breast cancer, 60-69]. Another participant noted that "*the outcomes that are important to you depend on the type of cancer you have*" [#5, female, breast cancer, 60-69]. Participant 4 also explained that she felt more able to cope with her cancer treatment outcomes because she lived in a city and therefore had relatively easy access to support, identifying geographical location as another factor influencing what outcomes are of importance.

Alignment of views

Another theme that came out of the first focus group was an apparent misalignment between outcomes that are important to patients and outcomes that are important to clinicians and researchers. As one participant explained, "*the outcomes that researchers and clinicians are*

interested in are not the same as the outcomes that patients are interested in" [#1, male, lung cancer, 70+]. Furthermore, because of this misalignment of views, another participant noted that "*patients are concerned about reporting side effects in case they get removed from the treatment as a result*" [#5, female, breast cancer, 60-69]. The majority of the participants agreed that they would be willing to deal with the side effects of a drug if it extended their life expectancy.

Data collection and causality

The group agreed that there needs to be better data collection and collaboration across the system in order to develop a stronger evidence base and provide more clarity around their treatments, to better understand the outcomes of the medicines they receive. One patient even stated "*I carry my own medical notes around with me*" [#1, male, lung cancer, 70+], because he is receiving treatment from two separate organisations, neither of which shares their notes on him with the other.

Even if there were better data collection and collaboration across the system, one patient argued that "*it is very hard to find causality when considering the pink petals [functioning]*" [#4, female, breast cancer, 60-69]. This, she felt, would make it particularly difficult to include 'functioning' outcomes in any OBP scheme.

Conclusions

In summary, the resulting key outcomes that were most important to focus group 1 participants were:

- Life extension
- Quality of life
- Side effects/toxicity
- Adverse events
- Environment within which the drug is administered
- Impact on family members

Although the six outcomes above were specifically identified as the most important by the participants in the first focus group, all of the petals in the outcome flower shown in **Error! R eference source not found.** were identified as important to at least one of the participants.

Beyond the main high-level outcomes of importance, the group also raised other important issues. Firstly, participants had difficulty separating the outcomes of their drug treatment from the outcomes of their continuum of cancer treatment. This suggests it is important to consider the impact of any cancer drug within the wider context of an individual's overall cancer experience. Secondly, heterogeneity exists in the outcomes of importance depending on context-specific factors, which are important to acknowledge when considering which outcomes are important to whom.

Thirdly, patient views do not always align with researcher and clinician views on what outcomes are of importance. Research, like that which we have undertaken, can attempt to synthesise a range of stakeholder views, therefore identifying commonalities and priorities to overcome misalignments in order to produce a core set of outcomes that are important for all when creating an OBP scheme. Finally, participants felt that there needs to be a greater level of data collection and collaboration; an OBP scheme that created accountability would help to stimulate such an environment.

Focus Group 2

Method

The second focus group used a card sort technique similar to that employed in cognitive psychology.[87] The participants were split into pairs and presented with 34 specific treatment outcomes on individual A5-sized cards. In their pairs they were asked to order the 34 outcomes into a diamond structure, with the 'most important' outcome(s) at the top of the diamond and the 'least important' outcome(s) at the bottom. The diamond shape imposed an expectation that there would be more cards placed in the middle at fairly important and less at the extremes, thus challenging the participants to work together to effectively prioritise.

As well as ranking the 34 pre-identified outcomes in this way, participants were also invited to highlight any outcomes they felt were missing from this list and rank them accordingly. They were also encouraged to combine/conflate outcomes they thought were similar constructs. This technique reduced the number of outcomes while taking into account the dimensions of quality of life cancer patients deemed to be important as an underlying theoretical model.

Views of Focus Group 2

Outcomes of importance

The final layout of outcomes from pair 1 are shown in Figure 9, with the final rankings from pair 2 displayed in Figure 10. The Figures reproduce the positioning of their cards by each pair respectively. The most important outcomes to that pair are in the top row of each Figure and the least important outcomes are in the bottom row. There is no significance to the relative position of individual outcomes within each row of each figure.

Comparing Figure 9 with Figure 10 it is clear that although there is consensus across the two subgroups with respect to the relative importance of certain outcomes, there is also disagreement about others. Overall, the discussion on outcomes of importance in the two pairs can be summarised in five categories: life extension and quality of life; side effects; emotional functioning; impact on family; and satisfaction with the treatment.

Pair 2 ranked life extension as an 'important' outcome, particularly because of its direct link to hope. It was claimed that '*hope is like life extension*' because without the existence of potential life extension hope suffers. Pair 1 also acknowledged the importance of life extension, but went on to argue that patients also want '*a good quality of life*'. This, they felt, was just as important as life extension and led them to rename the outcome 'normalised life extension'. In their mind, returning to a sense of normality (i.e. returning to normal activities, returning to work and regaining mobility) were good determinants of quality of life that feed into normalised life extension. Pair 2 agreed that it is not just about returning to work, for example, but about '*returning to normality*' more broadly.

Both pairs agreed that all of the individual outcomes describing side effects could be grouped into broader side effects outcomes. Pair 2 listed the individual side effect outcomes under a single 'side effects' category and ranked it as 'less important'. This was partly because of how well many side effects, particularly pain, are now managed. However, pair 1 argued that there are two distinct types of side effects: '*short term in-treatment side effects and long term after-treatment side effects*'. Short term in-treatment side effects were regarded as 'less important' as patients are willing to '*put up with them if the treatment keeps you alive*'. On the other hand, long term after-treatment side effects were ranked as 'important' because of their lasting effects.

Anxiety, depression, lack of hope and lack of confidence were all combined by pair 1 and classed as 'fairly important'. According to participant 6 & 7, these outcomes should all be '*grouped together and could be included as a sentence [in the survey]*'. They went on to decide that these were 'fairly important' outcomes. Similarly to pair 1, pair 2 combined depression, anxiety and social support/loneliness under the emotional wellbeing outcome, ranking these as 'important'. All of these specific outcomes fall under the wider emotional functioning heading in the outcomes flower, Figure 8, suggesting that cancer patients are comfortable viewing these outcomes as a single, wider emotional functioning or emotional wellbeing outcome.

Pair 1 and pair 2 both grouped burden on loved ones and relying on caregiver/family under the impact on family outcome. The second pair acknowledged that cancer in general is '*a burden on loved ones, children and parents*'. They then went on to discuss how the cancer treatment itself could impact on their family, for example through changes in appearance and the impact this could have on a patient's child. Overall, pair 1 ranked impact on family as 'important'. Interestingly, although impact on family was important to both participants in pair 1, they classed it as 'out of scope'. They explained this by stating '*the impact on family comes from the diagnosis and not the treatment, therefore it is out of scope*'.

Satisfaction with treatment was regarded as 'important' by pair 2. Participant 9 explained how they wanted to undergo their cancer treatment at home, but because they were unable to inject themselves they had to visit a health professional for it to be administered. It was then suggested that satisfaction might come under quality of care, which could be an outcome in its own right but is not for the most part a consequence of the medicine used and therefore is out of scope for an OBP scheme for a medicine. Unlike the second pair, pair 1 argued that '*satisfaction with the treatment is peripheral*' and therefore ranked as 'least important' compared to the other outcomes.

Finally, pair 2 created a new category, 'coping', which includes hearing, speech, tiredness and so on, and ranked it as the 'most important' outcome. But separating out the role of the medicine from the wider cancer experience would be difficult.

While the most important outcomes appear to differ across to the two pairs when comparing Figure 9 with Figure 10, they both suggest that 'normality' is important: returning to normal activities, returning to work mobility, avoiding recurrence (pair 1) and coping, communicating, sleeping and confidence (pair 2). In terms of those outcomes that were least/less important, these are the outcomes that are either side effects of the treatment or consequences of the cancer diagnosis, this reflects the opinion that many patients put up with the treatment if it keeps them alive.

Figure 9: Pair 1 ranking of outcomes

Most important		Return to normal activities of daily living Return to work Loss of mobility	(Normalised) life extension* Recurrence of cancer Fear of recurrence	
Important		Long-term side effects* Hearing/talking Infertility	Having to undergo surgery again	
Fairly important		Sexual relationships, sexual functioning and/or libido	Anxiety Depression Lack of hope Lack of confidence	
Less important		Short-term side effects* Memory loss Tiredness Difficulty sleeping Weight loss Lack of concentration	Infection	Other side effects* (not categorised by respondents as either long or short term) Incontinence Constipation or loose stools Decreased appetite Feeling sick Pain
Least important		Having to go to hospital or A&E as a consequence as your treatment	Satisfaction with the treatment (e.g. time spent, how it is administered)	Having to go to hospital or A&E as a consequence of your treatment
Out of scope	Impact on family Relying on a caregiver/family Burden on loved ones	Social support/loneliness	Frustration/annoyance/anger	Emotional wellbeing

* denotes new outcomes, or outcome categories, identified by participants

Figure 10: Pair 2 ranking of outcomes

Most important			Coping* Hearing/speech Tiredness Frustration/annoyance/ anger Lack of confidence		
Important	Satisfaction with the treatment (e.g. time spent, how is administered) Having to undergo surgery Having to go to hospital or A&E	Fear of recurrence Recurrence of cancer	Life extension Lack of hope	Emotional wellbeing Depression Anxiety Social Support/Loneliness	Impact on family Burden on loved ones Relying on caregiver/family
Fairly important		Loss of mobility/ autonomy*/independence*	Return to work	Return to normal ADL	Infertility
Less important		Side effects* Weight loss Memory loss Lack of concertation Satisfaction with appearance Difficulty sleeping Infection Decreased appetite Incontinence Feeling sick Constipation/loose stools Sexual relationship/ function	Understanding the benefits* (health literacy and communication with doctors)		
Least important		Body confidence*	Pain		

* denotes new outcomes, or outcome categories, identified by participants

Other areas of discussion

Heterogeneity in outcomes of importance – context matters

As in the first focus group, all participants in focus group 2 agreed that heterogeneity exists in the outcomes of importance, depending on the situation of the patient in question. In the first subgroup it was stated that '*the age and family status of patients need to be understood when trying to understand what outcomes are of importance to them*'. For example, they noted that infertility is likely to be of greater importance for younger patients, and the importance of sexual relationships also depends on age '*as well as cancer and drug type*'.

Subgroup 2 in the second focus group also felt that '*outcomes are situation dependent, including diagnosis and care pathway*'. In particular, they regarded life extension as more important to younger patients, or to those that have children to care for. Likewise, they also linked the importance of infertility to age.

Causality

Issues around causality were again raised in focus group 2, as they were in focus group 1. However, in focus group 2, causality was discussed in slightly different contexts across the two subgroups. Subgroup 1 argued that many of the 34 outcomes being considered are '*not related to the drug that you receive, and are outcomes of the diagnosis itself*'. Many of the outcomes were not deemed to be causally linked to the cancer medicines and so were classed as out of scope, as shown in the bottom row of Figure 9.

In subgroup 2 the causal link between different outcomes was also discussed, for example the causal link between '*emotional wellbeing and appearance, as well as isolation*'. Later in the discussion other causal links between outcomes were discussed. Participants 8 and 9 felt that reoccurrence is causally linked to a patient's emotions, as is hearing, speech and mobility. Moreover, fear of recurrence is causally linked to outcomes such as weight loss.

Health literacy

A detailed discussion on health literacy occurred in group 2. In particular, the importance of health literacy among patients was discussed, particularly when communicating with health professionals who often present information in technical terms. Health literacy was deemed important to understand such information, but notably is not an outcome in its own right.

Conclusions

Figure 9 and Figure 10 outline in detail how important each of the outcomes is to subgroup 1 and subgroup 2 respectively. In general, taking both subgroups' views together, the outcomes of most importance can be summarised as: life extension and quality of life; side effects; emotional functioning; impact on family; and satisfaction with the treatment. In some areas there was agreement across the subgroups, for example with respect to the importance of life extension, quality of life, and emotional functioning. However, views also varied across the subgroups with respect to the importance of the impact on family and of satisfaction with the treatment.

As in the first focus group, heterogeneity in outcomes of importance and causality were also issues raised by participants in focus group 2. Based on the discussions in focus group 2, which built on the discussion in focus group 1, the ten most important types of outcomes to these cancer patients were identified by the research team, in no particular order, as:

- Long term after-treatment side effects
- Infertility
- Survival
- Satisfaction with treatment
- Progression/recurrence
- Return to normal activities of daily living
- Emotional wellbeing
- Having to undergo surgery again
- Impact on family and caregivers
- Short term in-treatment side effects

These outcomes were then included in a survey of patients with cancer, and carers of those with cancer, to explore which outcomes were of most importance to a larger sample of respondents. A detailed description of the survey methodology and findings can be found in Appendix 5.

Appendix 5 – Survey of Patients and Carers

Objective

An online survey of current and past patients with cancer, as well as current and past carers of someone with cancer, was carried out during August and September 2018. The objective of this survey was to gain a broader understanding of what treatment outcomes matter most to cancer patients and their carers, building on the findings from the two focus groups (see Appendix 4).

Method

Survey design

The research team designed an online survey (see Appendix 5A) in SmartSurvey (version 4.10.1, SmartSurvey Ltd, 2018) through which cancer patients and carers could submit their preferences over the relative importance of the following ten treatment outcomes:

- Short term in-treatment side effects
- Long term after-treatment side effects
- Fertility problems
- Survival
- Satisfaction with treatment
- Progression, relapse or recurrence
- Return to normal activities of daily living
- Emotional wellbeing
- Having to undergo surgery again
- Impact on family and caregivers.

These ten outcomes were selected for inclusion in the survey based on the findings of the two focus groups with cancer patients (see Appendix 4). In the survey, respondents were asked to rank the ten outcomes from one, most important, to ten, least important. Note that the ten outcomes were randomly ordered for each respondent, mitigating any framing effect bias.

Information was also gathered on respondents' gender, age group and employment status. Respondents were also asked about their experience with cancer, in order to better understand whether different characteristics or experiences are associated with different outcome preferences. Respondents were asked:

- Whether they are a patient or carer, or both
- Which cancer(s) they had been diagnosed with

- How long since they were last diagnosed with cancer
- Which treatment(s) they had received for their cancer
- Whether the intention of that treatment was to cure or control their cancer.

Respondents who reported being a carer were asked the above questions with respect to the person they were or had been caring for, whereas respondents identifying as patients were asked about their own cancer. Individuals identifying as both a patient and carer were treated as patients. Those that reported being neither a patient nor a carer were thanked for their time and informed they were not eligible to participate in the study. Note that where respondents reported more than one cancer diagnosis, they were asked the time since diagnosis question in respect of their most recent cancer diagnosis.

The survey was piloted with the focus group attendees and members of the Steering Group. Ethical approval was received from the BDM RESC at King's College London, Ref: HR-17/18-5907.

Data collection

The survey was uploaded to the 'Patient Involvement at Cancer Research UK' section of the Cancer Research UK website on Wednesday 15th August 2018 and was open for four weeks, closing on Wednesday 12th September 2018. SmartSurvey reported 170 complete submissions and 83 partial submissions. The latter means that the respondent started but did not finish the survey. Their responses were not usable and so were excluded from the analysis. Six of the 170 respondents stated that they were neither a patient nor a carer and were therefore directed to the end of the survey. This left 164 complete responses from cancer patients and carers to be analysed.

It is not possible to estimate a response rate as it is not known how many people will have seen the advertisements for the survey. Equally, it is not possible to determine how far our sample of respondents is biased in a way that would affect the aggregate responses received. We note in the results section, however, that our sample of respondents was disproportionately female (88%) and that breast cancer was by far the most common cancer reported (by 61% of respondents). It is therefore clear that this survey does not capture a representative sample of cancer patients. The survey findings should therefore be treated as indicative within the cancer patient groups covered, rather than definitive.

Analysis

The number of respondents (164) is insufficient to warrant formal statistical tests. Our analysis of the survey responses is consequently essentially qualitative. However, in order to get a sense of the collective views of the respondents the average rank score of each outcome is presented (the sum of all ranks for an outcome across all the respondents, divided by the number of respondents). This is an approximation of the relative importance of the outcomes.

Caution should be taken when making any further inference of the rank score because it takes no account of whether, for example, the outcome ranked 1 was a lot, or only a little, more important than the outcome ranked 2, just that it was ranked higher; in other words, the ranking reflects ordinal rather than cardinal preferences. The frequency of rankings, how often each outcome was ranked at each level, is also explored.

The analysis initially considers the sample (all patients and carers) as a whole. In addition, we consider how these priorities vary depending on the experience the respondents have had with cancer. Specifically, the responses were analysed for variations by patient and carer experience, cancer site, time since diagnosis, type of treatment received and the intention of the treatment. Analysis was only undertaken on subgroups with n>15 (i.e. subgroups representing 10% or more of the respondents). The role of personal characteristics – gender, age and employment status at the time of diagnosis – and their influence on rankings was also considered. Sub-group rankings are presented with the ordering based on the rankings across all respondents to allow for cross-comparison.

Findings

Respondents' characteristics and experiences with cancer

The characteristics of the respondents, i.e. gender, age and employment status at diagnosis, are shown in Table 10. The vast majority (n=144) of the 164 respondents were female. Only 20 of the responses were from males. Among the respondents the most common age group was 51-60 years (58 respondents), followed by 61-70 years (n=41) and 41-50 years (n=38) respectively. The vast majority (n=128) of respondents were in employment at the time of the cancer diagnosis (full-time, part-time or self-employed), with six being students, five being unemployed and 16 being retired.

Table 10: Respondents' characteristics

Question	Response	Sample size (n)	Percentage
What is your gender?	Female	144	87.8%
	Male	20	12.2%
What is your age?	18-30 years	5	3.1%
	31-40 years	18	11.0%
	41-50 years	38	23.2%
	51-60 years	58	35.4%
	61-70 years	41	25.0%
	71-80 years	4	2.4%
	81-90 years	0	0.0%
	Older than 90 years	0	0.0%
What was your employment status immediately prior to diagnosis?	Full-time employment	84	51.2%
	Part-time employment	26	15.9%
	Self-employed	18	11.0%
	Unemployed	5	3.1%
	Retired	16	9.8%
	Student	6	3.7%
	Other	9	5.5%

Percentages may not add up to 100% due to rounding

Table 11 breaks down the experiences that respondents have had with cancer. The vast majority (n=144) were patients, with the other 20 reporting to be carers. The majority (n=100) of individuals had experienced breast cancer, with lung and bowel/colorectal cancer being the equal second most common, with 16 respondents each reporting the condition. It is worth noting that patients can be diagnosed with more than one cancer. A slight majority (n=85) of respondents were last diagnosed one to five years ago, or caring for someone last diagnosed one to five years ago.

The majority of respondents had undergone, or cared for someone who had undergone, surgery (n=127), chemotherapy (n=117) and radiotherapy (n=111), with a substantial minority receiving hormone therapy (n=77). Again, it is worth noting that patients typically receive more than one treatment. The purpose of these treatments was curative for the majority (n=118) of respondents, or the person the respondent was caring for; with 39 respondents reporting that the treatment was designed to control the cancer rather than cure it.

Table 11: Respondents' experiences with cancer

Question	Response	Sample size (n)	Percentage
Are you a patient or carer?	Patient	144	87.8%
	Carer	20	12.2%
Which cancer(s) have you/ they been diagnosed with?	Breast cancer	100	61.0%
	Prostate cancer	7	4.3%
	Lung cancer	16	9.8%
	Bowel/colorectal cancer	16	9.8%
	Melanoma skin cancer	1	0.6%
	Non-Hodgkin lymphoma	2	1.2%
	Kidney cancer	6	3.7%
	Head and neck cancer	7	4.3%
	Brain or other central nervous system cancer	6	3.7%
	Bladder cancer	0	0.0%
	Pancreatic cancer	2	1.2%
	Leukaemia	4	2.4%
	Other	15	9.2%
How long is it since you/they were last diagnosed with cancer?	Less than 1 year	32	19.5%
	1 to 5 years	85	51.8%
	More than 5 years	47	28.7%

Percentages may not add up to 100% due to rounding. Respondents can have multiple cancers and receive multiple treatments.

Table 11 (cont.): Respondents' experiences with cancer

Which treatment(s) have you/they received for your/ their cancer?	Surgery	127	77.4%
	Radiotherapy	111	67.7%
	Chemotherapy	117	71.3%
	Immunotherapy	9	5.5%
	Biological therapy	21	12.8%
	Hormone therapy	77	47.0%
	Other	31	18.9%
What is the purpose of the treatment?	Cure the cancer	118	72.0%
	Control the cancer	39	23.8%
	Other	7	4.3%

Percentages may not add up to 100% due to rounding. Respondents can have multiple cancers and receive multiple treatments.

Outcome priorities: across all respondents

Respondents were asked to rank in order of importance the ten outcomes listed below, which were those identified in the focus group discussions (Appendix 4) as likely to be the ten most important to cancer patients. The average rank score and equivalent rank of each of the ten outcomes across all 164 respondents is shown in Table 12. The outcomes have been ordered by rank score. Respondents were asked to rank the outcomes from 1, most important, to 10, least important. Therefore, the lower the score the more important the outcome is. For example, the outcome 'survival' scored 1.98, which is lower than any of the other outcomes and is therefore ranked as 1, the most important of the outcomes.

Table 12: Average outcome ranking and score across all participants

Rank	Outcome	Score
1	Survival	1.98
2	Progression, relapse or recurrence of your cancer	2.40
3	Long-term side effects	4.39
4	Return to normal activities of daily life	4.55
5	Short-term side effects	5.80
6	Emotional wellbeing	6.05
7	Satisfaction with treatment	6.73
8	Impact on family and caregivers	6.98
8	Re-surgery	6.98
10	Fertility problems	9.15

Across the whole sample, 'survival' and 'progression, relapse or recurrence' scored noticeably better than the other eight outcomes, and thus appear to be the two most important outcomes. 'Long-term side effects' and 'return to normal activities of daily life' ranked third and fourth respectively, being the next cluster of outcomes in terms of their score.

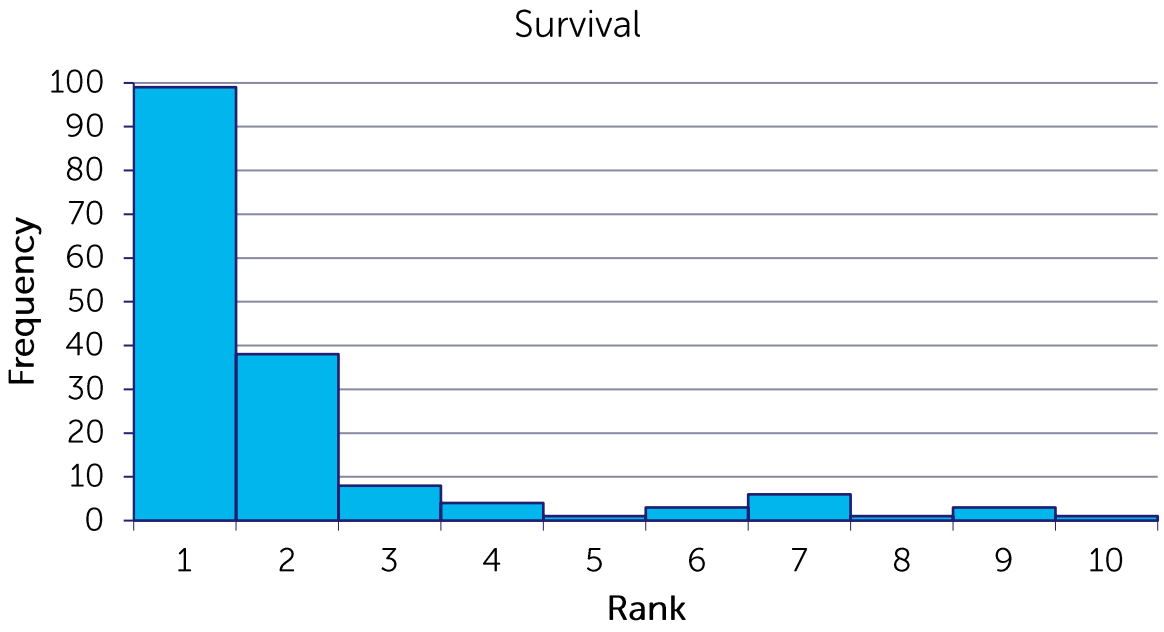
There is a relatively small difference in scores amongst the outcomes from 'short-term side effects', ranked fifth, to 're-surgery', ranked ninth. These five outcomes ('short-term side effects', 'emotional wellbeing', 'satisfaction with treatment', 'impact on family and caregivers', and 're-surgery') appear to form another cluster of outcomes. Finally, 'fertility problems' scored significantly worse than all other outcomes, appearing to be clearly the least important outcome of the ten.

Although Table 12 provides an overview of the ranking of outcomes across the sample, it does not give an insight into the frequency distribution of rankings for each outcome.

Figures 11 to 20 show the frequency distribution for each of the ten outcomes, i.e. how often each outcome was ranked at each level. For example, long-term side effects were ranked third by 50 respondents and this was the most common ranking of the outcome, as is shown in Figure 13.

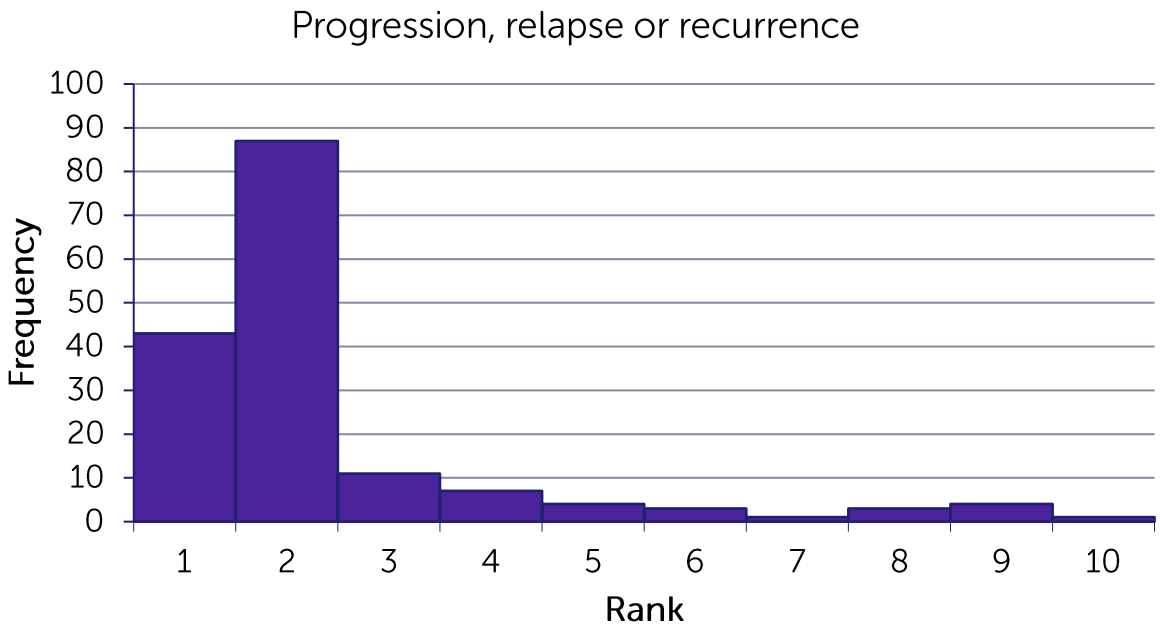
The frequency distribution of the survival outcome is positively skewed, as would be expected from the outcome deemed most important. Figure 11 shows that the majority of respondents ranked survival first, and of those that did not the majority that remained ranked it second.

Figure 11: Survival frequency distribution by rank



Similarly, the frequency distribution of progression, relapse or recurrence is also positively skewed, as shown in Figure 12. The majority of respondents ranked the outcome as second most important, with the next most common ranking being most important.

Figure 12: Progression, relapse or recurrence frequency distribution by rank



Long-term side effects and return to normal activities both have similar frequency distributions, as shown by Figure 13 and Figure 14 respectively. The most common ranking for both outcomes was third, followed by fourth. However, slightly more respondents ranked long-term side effects as third.

Figure 13: Long-term side effects frequency distribution by rank

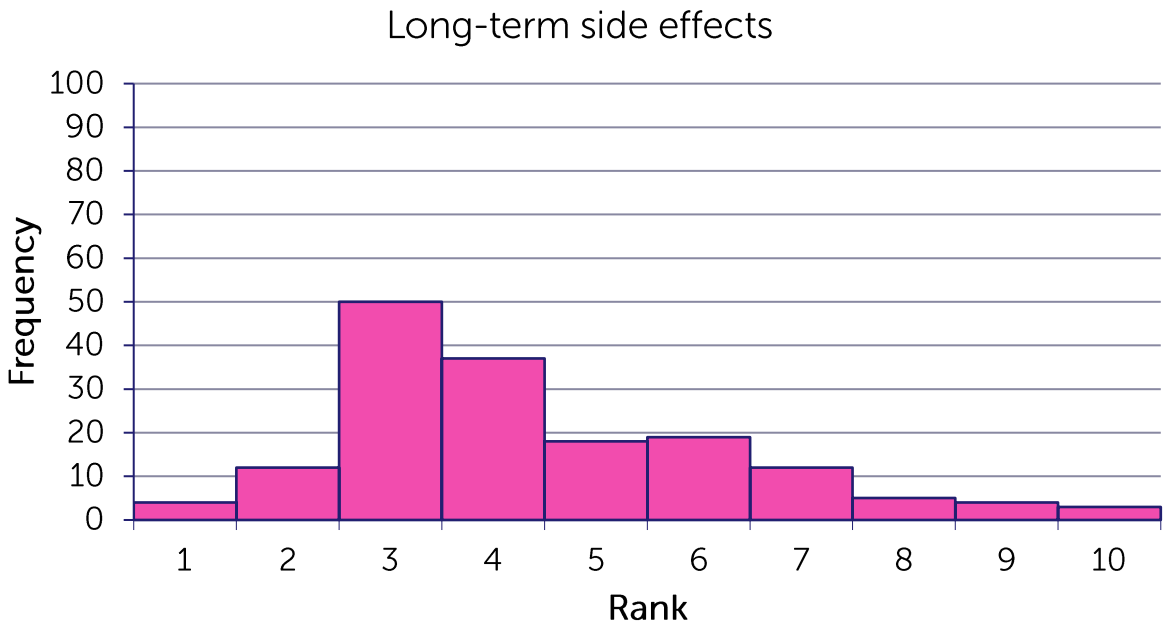
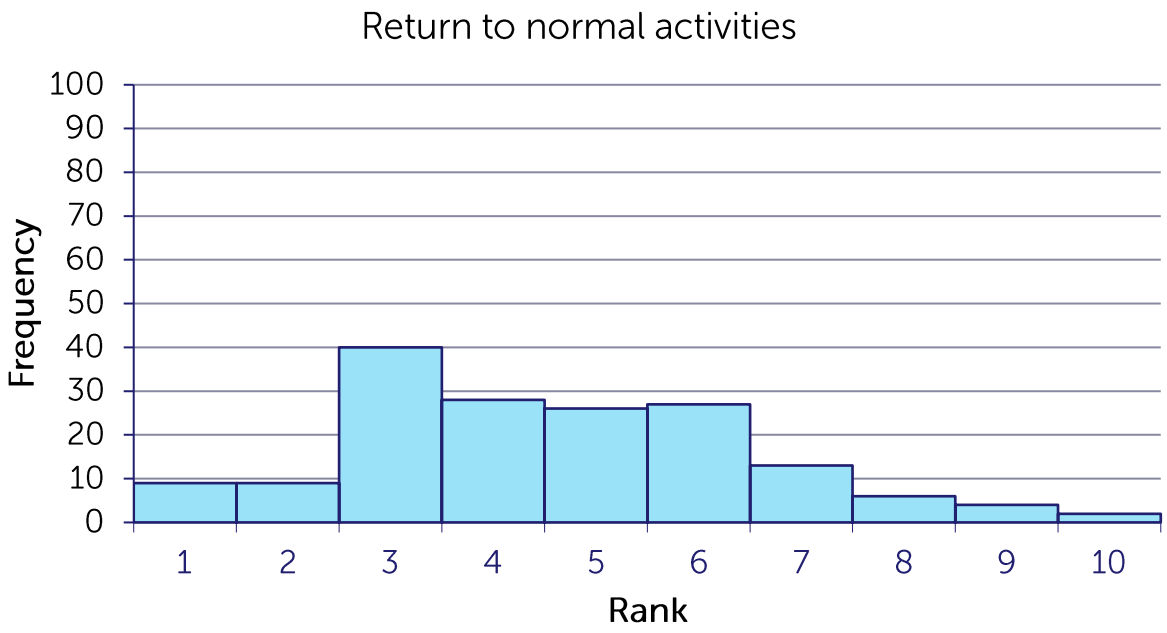


Figure 14: Return to normal activities frequency distribution by rank



Figures 15 and 16 show that short-term side effects and emotional wellbeing also have similar frequency distributions. The frequency distribution is relatively evenly spread across the ranks from three to nine.

Figure 15: Short-term side effects frequency distribution by rank

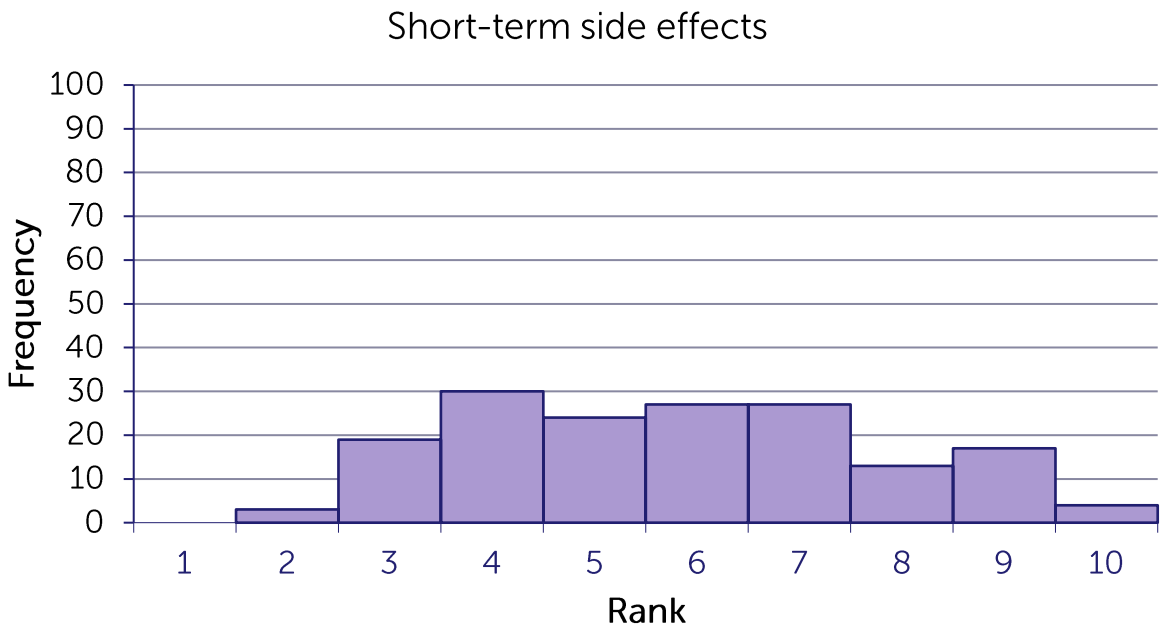
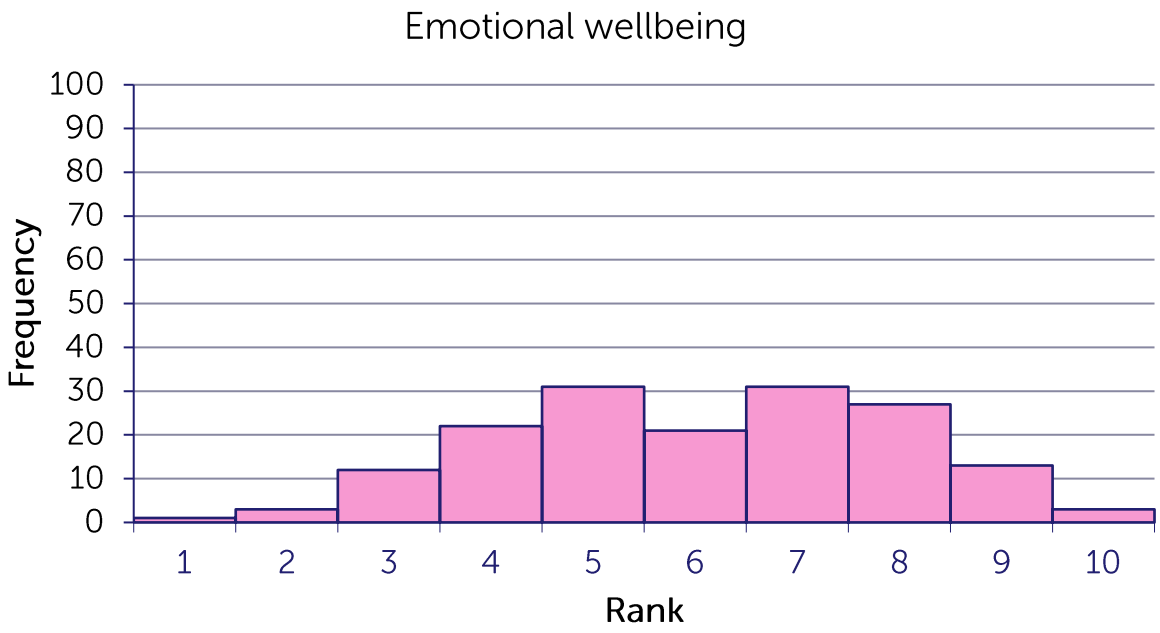


Figure 16: Emotional wellbeing frequency distribution by rank



Rankings of five and below were most common for satisfaction with treatment, with a relatively even distribution of responses across the ranks from five to ten, as shown in Figure 17.

Figure 17: Satisfaction with treatment frequency distribution by rank

Even lower rankings are more frequent among the impact on family and re-surgery outcomes, with the most common rank being eight and nine respectively. However, responses were still spread widely across numerous ranks, as shown in Figures 18 and 19.

Figure 18: Impact on family and caregivers frequency distribution by rank

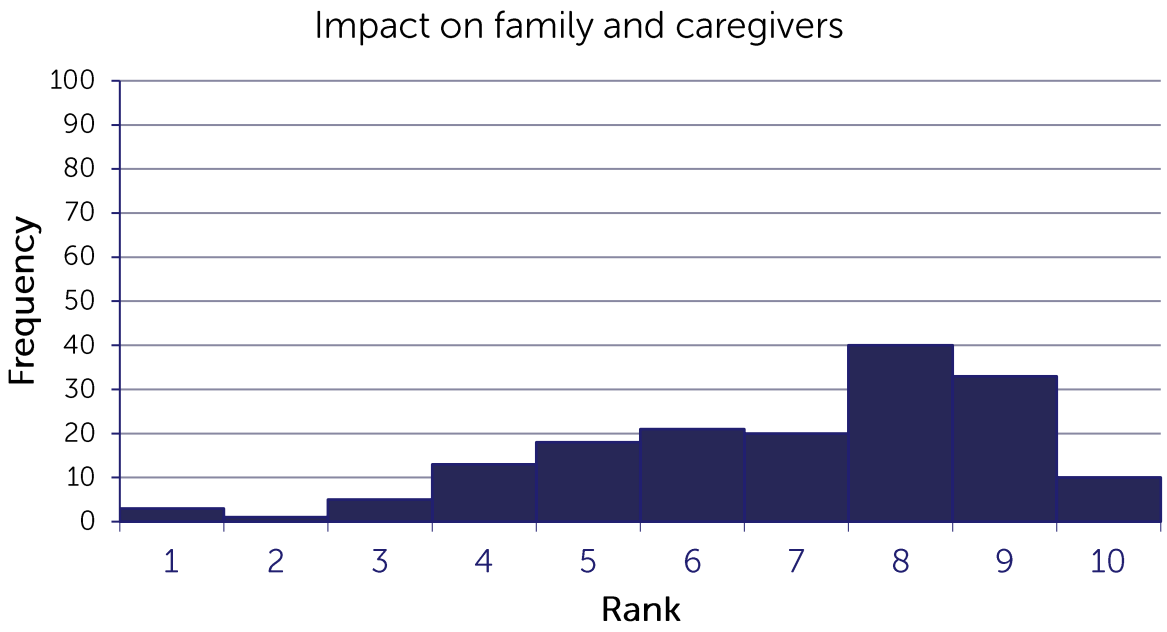
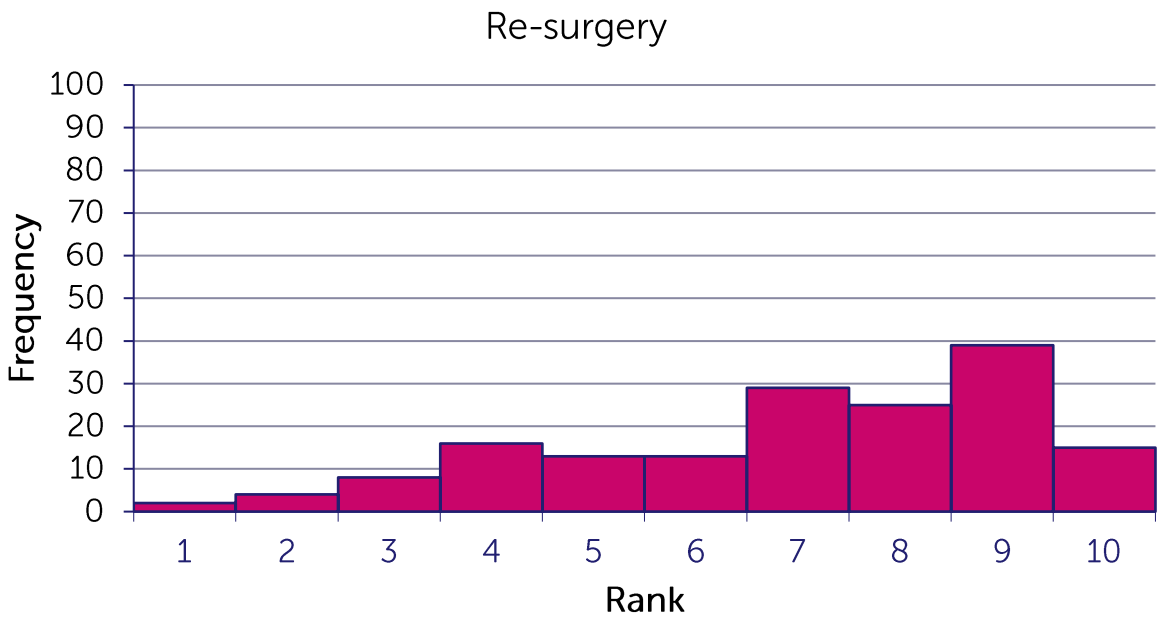
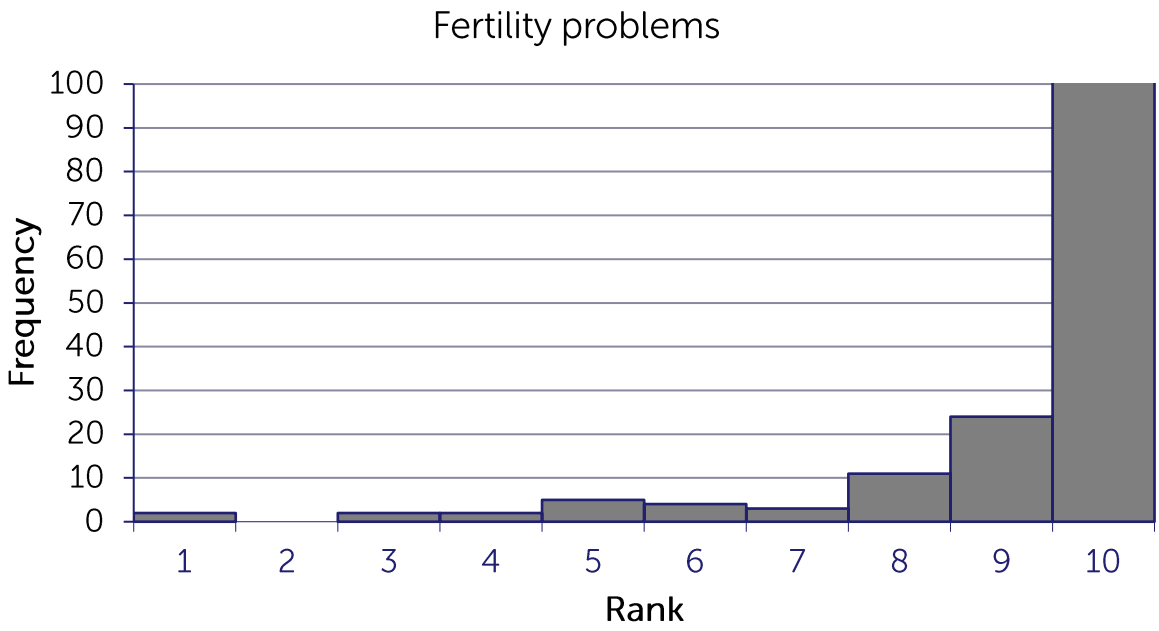


Figure 19: Re-surgery frequency distribution



Finally, the frequency distribution of fertility problems is considerably negatively skewed, as shown in Figure 20. The majority of respondents ranked it tenth, least important, with the next most common rank being ninth. However, this may be a result of the types of patients and carers who responded to the survey, which will be explored in more detail later.

Figure 20: Fertility problems frequency distribution



These findings suggest that survival is the outright most important outcome to respondents, with progression, relapse or recurrence being the clear second most important. Long-term side effects and returning to normal activities appear to be the next most important outcomes, although there was a much wider spread of rankings when compared to survival and progression, relapse or recurrence.

Likewise, there was much greater variability in responses across short-term side effects, emotional wellbeing, satisfaction with treatment, impact on family and caregivers, and re-surgery. Although lower ranks were most common for satisfaction with treatment, impact on family and re-surgery. Finally, there does appear to be a consensus that fertility problems is the least important outcome of the ten.

It is important to note that these rankings are likely to be highly dependent on the characteristics and experiences of those responding to the survey, and this is therefore explored in the next section.

Outcome priorities: association with respondents' cancer experiences

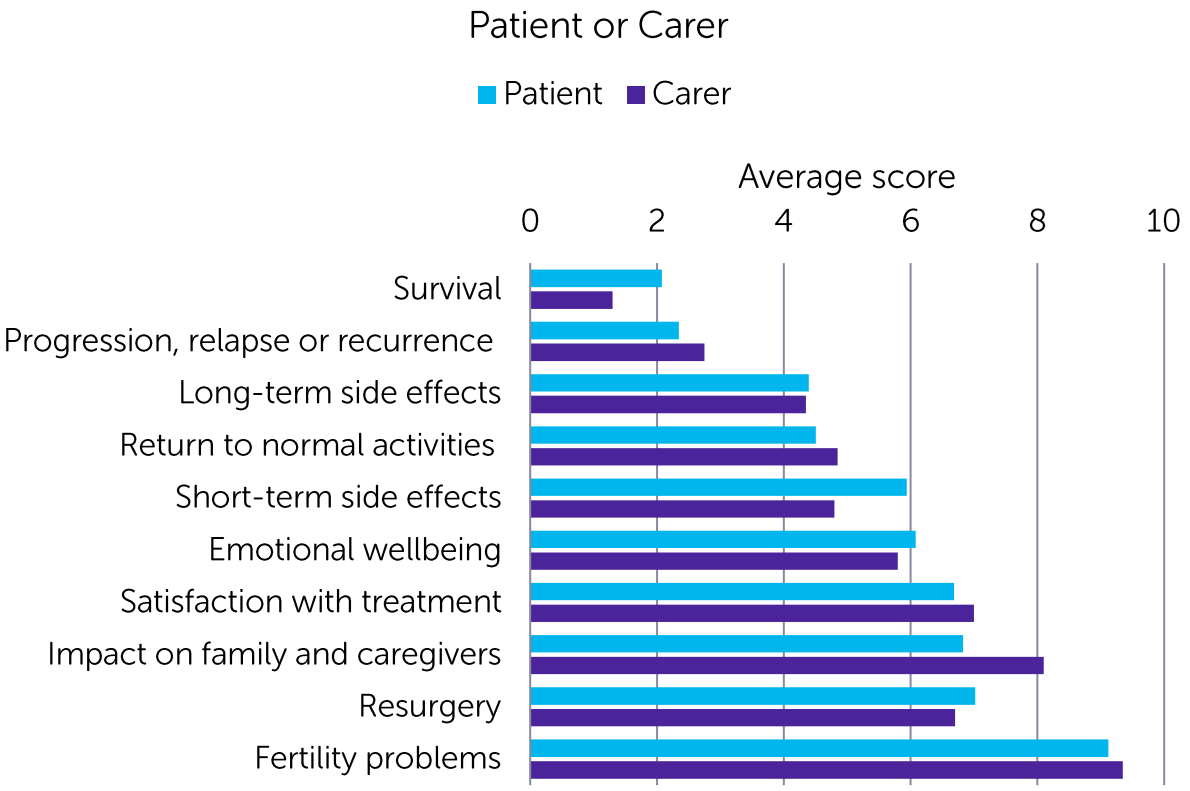
The analysis of variations in sub-groups by: patient and carer experience; cancer site; time since diagnosis; type of treatment received; and the intention of the treatment, considered the average rank score.

Figure 21 provides a visual representation of the average rank score provided for each outcome by patients (n=144) and by carers (n=20) respectively. The outcomes in the y-axis of this figure are ordered based on the rankings across all participants, shown in Table 12 above, to allow for easy cross-comparison. The lower the average score the more important the outcome, meaning that smaller bars related to more important outcomes.

The top three most important outcomes are the same for patients and carers alike, as shown in Figure 21.

However, carers appear to assign a greater value to the survival of the person they are caring for than patients do themselves. Interestingly, patients rank impact on family and caregivers as more important than carers do. On the other hand, carers perceive short-term side effects and re-surgery as more important than patients do.

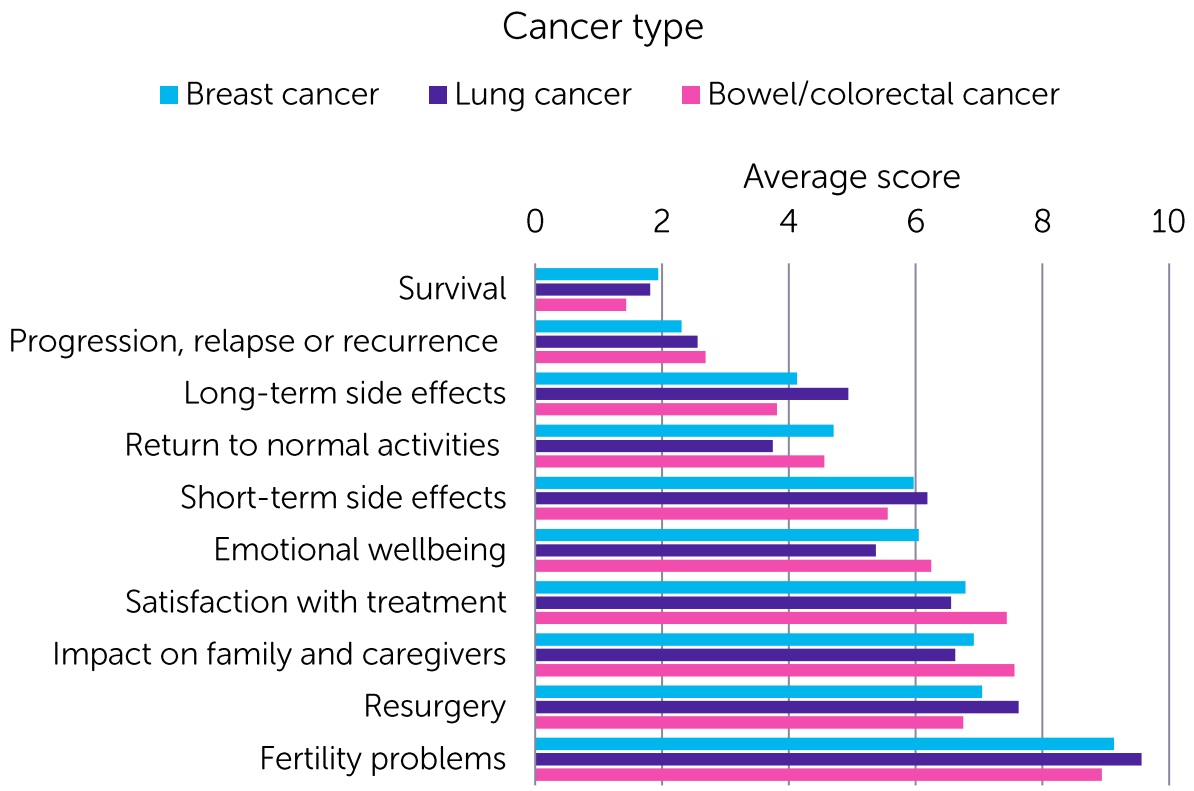
Figure 21: Average score of outcomes among patients and carers



There is a notable degree of agreement in rank scores across all three major cancer types. Survival and progression were the two most important outcomes among all three cancer type subgroups, as shown in Figure 22 below.

Interestingly, lung cancer patients and carers (n=16) rank return to normal activity as the third most important outcome, whereas breast (n=100) and bowel/colorectal cancer (n=16) patients and carers rank long-term side effects as the third most important. Further, bowel/colorectal cancer patients and carers are less concerned with impact on family and satisfaction with treatment, and more concerned with short-term side effects and re-surgery. Sample sizes were too small to compare any other cancer types.

Figure 22: Average score of outcomes among different cancer types



There is again a notable conformity in rankings regardless of time since diagnosis. Differences are once again modest. The top four outcomes in Figure 23 remain unchanged regardless of how much time has passed since diagnosis of the cancer.

However, those being diagnosed less than one year ago and their carers appear a little less concerned about satisfaction with the treatment, and place slightly greater weight on returning to normal daily activities. Those diagnosed more than five years ago are slightly more concerned with re-surgery, but still only rank it seventh.

Figure 23: Average score of outcomes among different times since diagnosis

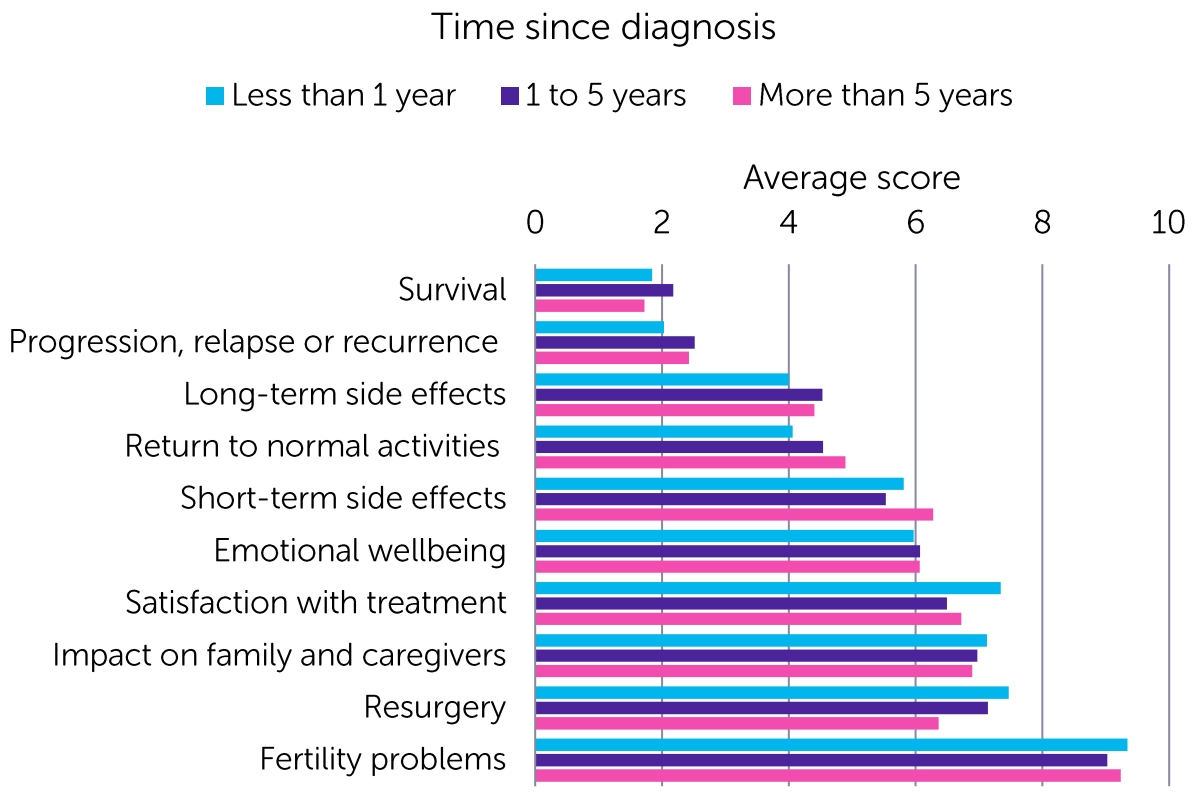
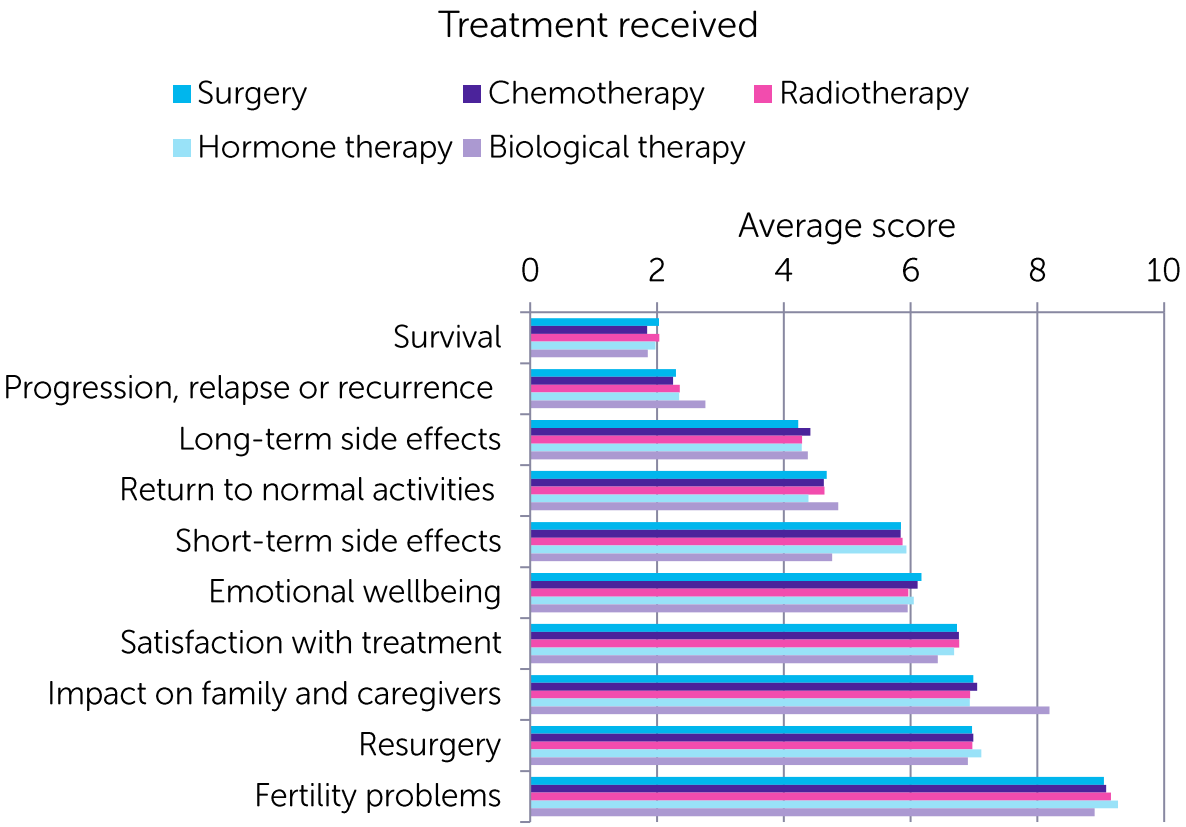


Figure 24 shows that preferences do not vary greatly according to the type of treatment received. However, it is important to note that patients can receive more than one treatment, meaning that numerous respondents are likely to be represented across multiple treatment types.

Patients and carers of those receiving biological therapy appear to be less concerned with the impact on family, and more concerned with short-term side effects compared to the other subgroups.

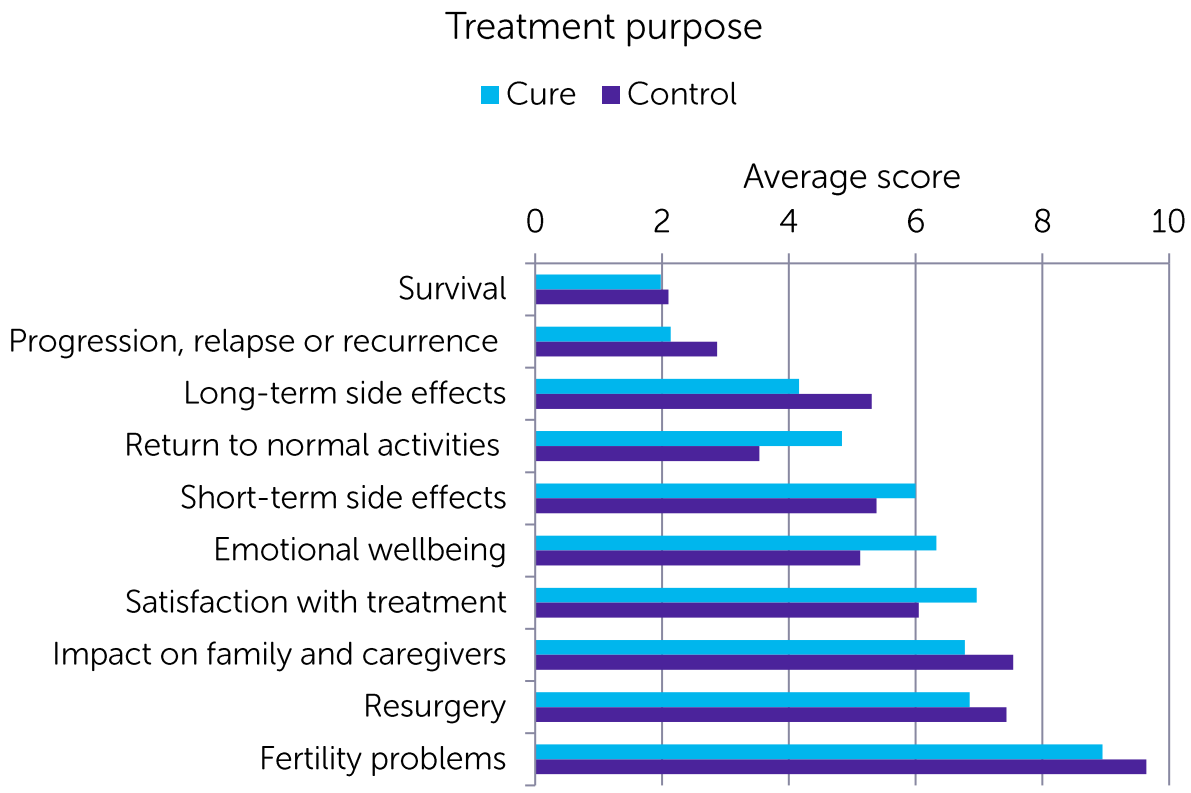
Figure 24: Average score of outcomes among different treatments received



Treatment intention appears to be one area within which preferences vary across respondents, as displayed in Figure 25, although the small sample size means that the differences can only be assessed qualitatively.

Again, survival and progression are the two most important outcomes across subgroups. However, those receiving treatment (and caring for those receiving treatment) to control their cancer ranked return to normal activities above long-term side effects, and emotional wellbeing above short-term side effects. Overall, 'control' respondents appear to be more concerned with 'getting back to normal', e.g. return to normal activities, short-term side effects and emotional wellbeing, than were 'treatment' respondents.

Figure 25: Average score of outcomes among different treatment intentions



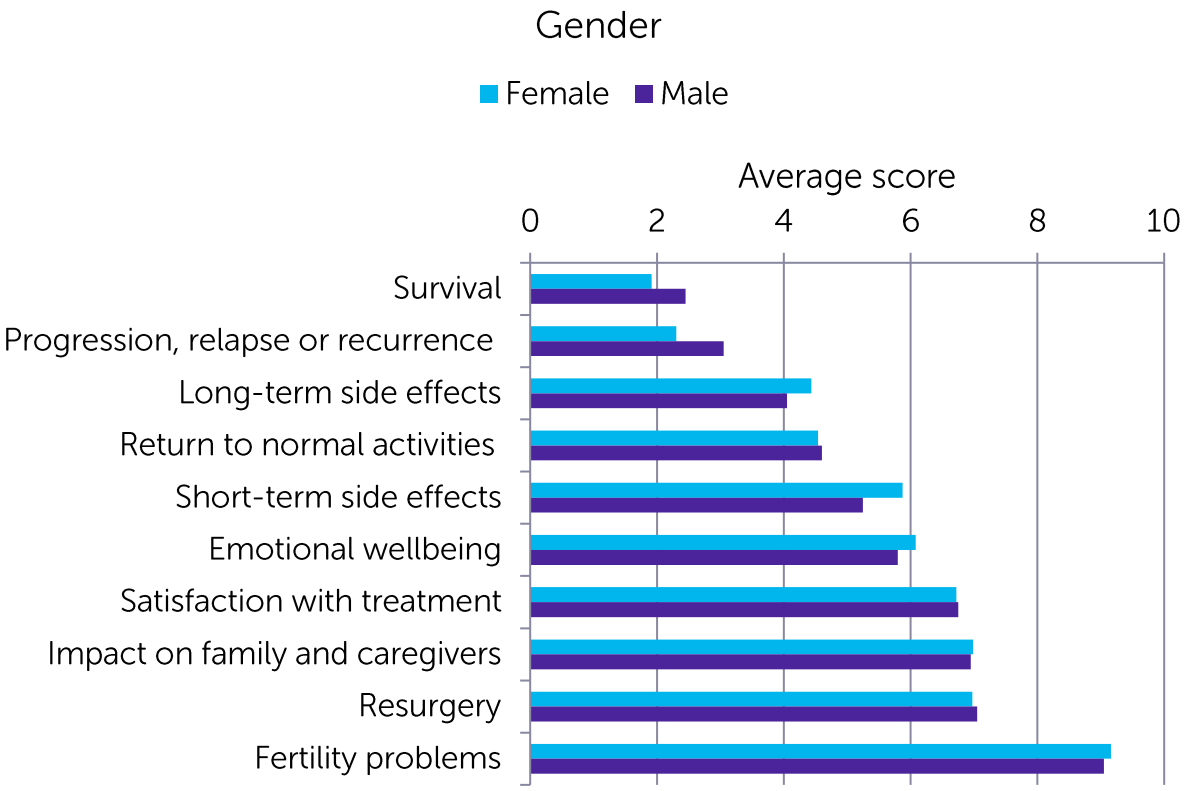
Overall, there were only limited differences in the preferences of individuals who have had different experiences with cancer. In general, survival, progression and long-term side effects were the outcomes of most importance. However, those receiving treatment (and caring for those receiving treatment) to control their cancer ranked return to normal activities as their third most important outcome. Most variance in preferences was observed among outcomes ranked from fifth to ninth, which was to be expected given the frequency distributions observed in the overall data.

Outcome priorities: association with respondents' characteristics

Figure 26 demonstrates that preferences do not appear to vary much by gender, although this finding should be treated with caution as only 20 of the 164 respondents were men.

The only difference in the rankings of the ten outcomes is that women rank re-surgery slightly higher than impact on family, whereas the opposite is true for men. It also appears that men are slightly more concerned with long- and short-term side effects, while women are more concerned with survival and disease progression.

Figure 26: Average score of outcomes among different genders



There appears to be more variation in preferences across different age groups, as per Figure 27, but these differences are generally observed among outcomes ranked between fifth and tenth – i.e. those deemed less important.

For example, those aged 61-80 years appear to be more concerned with impact on family and short-term side effects than other age groups. On the other hand, those aged 18-40 years seem to put more weight on fertility problems than other age groups, as might be expected. However, fertility problems were still ranked as the least important by all three age groups.

Figure 27: Average score of outcomes among different age groups

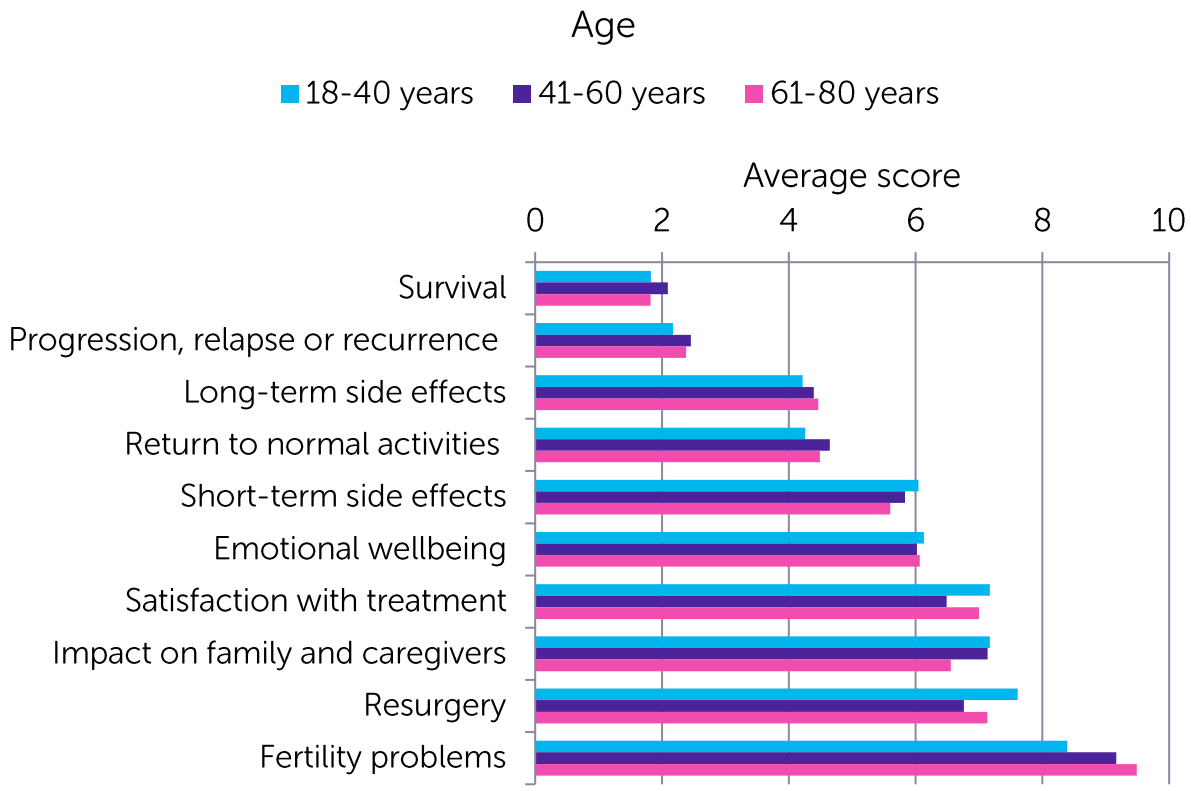
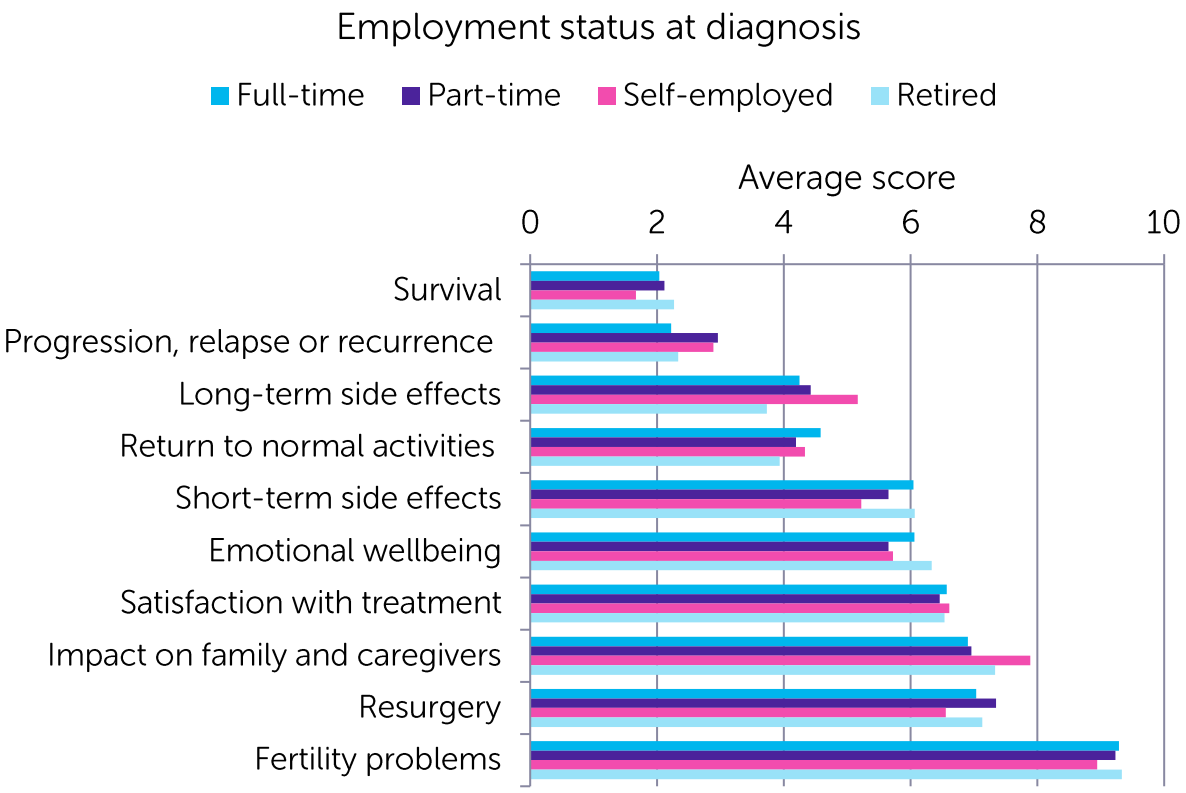


Figure 28 shows that there was some variation in preferences among different employment types.

Part-time (n=26) and self-employed (n=18) respondents both ranked return to normal activities as their third most important outcome, whereas for full-time (n=84) and retired (n=16) respondents it was long-term side effects. Self-employed respondents appear to be more concerned than other respondents with outcomes that are likely to impact their ability to work in the immediate future, such as short-term side effects and re-surgery.

Figure 28: Average score of outcomes among different employment statuses



Overall, preferences do not appear to vary significantly based on the gender or age of the respondent. There is slightly more variation in preferences across different employment statuses, with part-time and self-employed respondents both ranking return to normal activities as their third most important outcome, above long-term side effects.

Conclusions

Responses were collected from individuals with a wide range of experiences with cancer, as well as from individuals with a breadth of characteristics. This allowed analyses to be undertaken to help better understand: 1) how different experiences with cancer are associated with different preferences around treatment outcomes, and 2) how different characteristics are associated with different preferences around treatment outcomes.

Survival, and progression, relapse or recurrence of one's cancer, were consistently the first and second most important outcomes to patients and carers regardless of individual characteristics or experience with cancer.

In the majority of subgroups long-term side effects was ranked as the third most important outcome, with return to normal activities of daily life fourth. However, in some cases (e.g. those in part-time and self-employment) this ordering was switched.

The greatest variation in preferences across subgroups occurred amongst outcomes ranked between 5th and 9th, where there were often minimal differences in the average score of numerous outcomes. Finally, problems with fertility was ranked as the least important outcome regardless of individual characteristics or experience with cancer.

Annex 5A – Patient and carer survey

Your experiences with cancer

The following questions ask about your experience with cancer.

ASK ALL

1. What is your experience of cancer? *Please tick the category that applies to you.*
    a. I am now or have been a patient with cancer
    b. I am now or have been a carer of someone with cancer
    c. I am now or have been **both** a patient with cancer and a carer of someone with cancer
    d. Neither of the above

If you have experience of being a patient and a carer please complete the rest of the survey thinking about your experience as a cancer patient.

ASK ALL

2. Which cancer type(s) have you {/has the person you care [cared] for} been treated for? *Please tick the category or categories that apply to you.*

    a. Breast cancer
    b. Prostate cancer
    c. Lung cancer
    d. Bowel/colorectal cancer
    e. Melanoma skin cancer
    f. Non-Hodgkin lymphoma
    g. Kidney cancer
    h. Head and neck cancer
    i. Brain or other central nervous system cancer
    j. Bladder cancer
    k. Pancreatic cancer
    l. Leukaemia
    m. Other cancer, please specify:

ASK ALL

3. How long is it since you {/the person you are [were] caring for} were diagnosed? If you {/they} have {/[had]} received more than one diagnosis of cancer please answer for the most recent diagnosis. *Please tick the category that applies to you.*
    a. Less than 1 year
    b. 1 to 5 years

c. More than 5 years

d. Don't know/can't remember

ASK ALL

4. Which types of cancer treatment have {has [had]} you {/the person you are [were] caring for} received? *Please tick the category or categories that apply to you.*

a. Surgery

b. Radiotherapy

c. Chemotherapy

d. Immunotherapy

e. Biological therapy

f. Hormone therapy

g. Other, please specify:

ASK ALL

5. If known, what is [was] the purpose of the treatment {for the person you are [were] caring for? *Please tick the category that applies to you.*

a. The treatment aims [aimed] to cure my {/their} cancer

b. The treatment aims [aimed] to control my {/their} cancer

c. Don't know/can't remember

d. Other, please specify:

Important cancer outcomes

We know that most cancer treatments aim to cure the cancer or to prolong life, but that treatment can affect how patients feel and their quality of life. Through this survey we would like to understand the importance of these different factors and what matters most to patients when they're considering cancer treatment options.

The following questions ask about which outcomes from treatment are most important to you {/the person you care for}. While all of the outcomes may strike you as important, please consider carefully whether any of them are more or less important. There are no right or wrong answers; we would just like to know your views.

ASK ALL

6. When being offered a cancer medicine (e.g. chemotherapy, immunotherapy, targeted therapy or hormone therapy) which of the following factors were [or would be] of most importance to you {/the person you care for}? Please order the 10 outcomes from 1 (most important) to 10 (least important).

Please note:

- There are two ways you can order the outcomes:

1. Clicking on the dropdown box next to each outcome and selecting the number
2. Clicking on and dragging each outcome, putting them in your preferred order

- After you order your first outcome the survey will automatically order the remaining outcomes. Please the reorder them based on your views.

Outcome	Rank
Avoiding short-term (during treatment) side effects (like feeling tired, pain and/or numbness, having memory problems, diarrhea, incontinence, or hair loss)	
Avoiding long-term (post treatment) side effects (like having organ damage, loss of sexual function, persistent swelling, or bone density loss)	
Avoiding fertility problems (like having trouble getting pregnant)	
Improving your {their} chances of surviving	
Satisfaction with how the treatment is delivered (like the number of hospital visits, or how the medicine is given, e.g. tablet, patch or injection)	
Avoiding progression, relapse or recurrence of your {their} cancer (avoid cancer coming back or spreading)	
Being able to continue normal activities of daily life (including work, leisure activities, volunteering, family life)	
Improved emotional wellbeing (like not feeling depressed or anxious, not having low self-esteem)	
Avoiding the need to undergo surgery (not having a further operation to remove the cancer)	
Reduced strain on caregivers and family members	

If there are any **outcomes of importance** to you {/the person you care for} that are **not included above**, please list them here and indicate where they would rank: [OPEN TEXT]

Please check that you are happy with your ordering of the outcomes, shown below. If you are not please click “Previous page” and reorder them.

You also highlighted the following outcome(s) as important to you:

About you

The following questions ask some information about you {, not the person you care for}

ASK ALL

7. Are you… *Please tick the category that applies to you.*
    a. Male
    b. Female

c. Other

d. Prefer not to say

ASK ALL

8. How old are you? *Please tick the category that applies to you.*

    a. 18-30 years

    b. 31-40 years

    c. 41-50 years

    d. 51-60 years

    e. 61-70 years

    f. 71-80 years

    g. 81-90 years

    h. Older than 90 years

    i. Prefer not to say

ASK ALL

9. What was your employment status immediately before the cancer diagnosis {/of the person you are [were] caring for}? *Please tick the category that applies to you.*

    a. In full-time employment

    b. In part-time employment

    c. Self-employed

    d. Unemployed

    e. Retired

    f. Prefer not to say

    g. Other, please specify:

ASK ALL

10. Did your employment status change as a result of the {/their} cancer? *Please tick the category that applies to you.*

    a. Yes

    b. No

    c. Prefer not to say

ASK IF Q10='Yes' & Q3='Less than one year' OR 'Don't know/can't remember'

11. What is your employment status now? *Please tick the category that applies to you.*

    a. In full-time employment

    b. In part-time employment

    c. Self-employed

d. Unemployed
e. Retired
f. Prefer not to say
g. Other, please specify:

ASK IF Q10='Yes' & Q3= '1 to 5 years' OR 'More than 5 years'

12. What was your employment status <u>one year after</u> your {/their} initial cancer diagnosis?
Please tick the category that applies to you.

a. In full-time employment
b. In part-time employment
c. Self-employed
d. Unemployed
e. Retired
f. Prefer not to say
g. Other, please specify:

-- You have completed this survey! --

-- Thank you very much for taking the time to answer this survey, your response is extremely valuable to us. --

Appendix 6 – Health and Cancer Data in the NHS

The extent to which cancer outcomes data are already routinely collected in the NHS has been reviewed. Such data, if sufficiently complete and accurate, might form the foundation for more extensive or detailed data collection in support of OBP.

Within the NHS, real-world data for cancer care is derived from a range of structured and unstructured national datasets. Structured datasets broadly fall into three categories – activity data via Hospital Episode Statistics (HES), incidence data via the cancer registry and death data via the Office of National Statistics (ONS).

HES data are warehoused by NHS Digital. It is a database of all patient episodes at English NHS hospitals, and includes variables reflecting patient characteristics, diagnosis (ICD-10) and procedures (OPCS) and geographic details. HES was initially set up for hospital reimbursement purposes but it is now widely used for research and service evaluation. Data are available on admissions, outpatient appointments and emergency attendances.

Public Health England's (PHE) National Cancer Registration and Analysis Services (NCRAS) have records of every cancer patient diagnosed in England, submitted against the Cancer Outcomes and Services Dataset with linked records from the National Radiotherapy Dataset, and the Systemic Anticancer Therapy (SACT) dataset (all treatments that have an anti-cancer effect relating to chemotherapy, including hormones and bisphosphonates, oral chemotherapy, intravesical chemotherapy and targeted / biological therapies).

Mortality data are held by the ONS and include date, place and underlying cause of death.

The UK also has the Clinical Practice Research Datalink (CPRD) which consists of electronic health records (EHR) from a network of general practices (GPs) across the UK (i.e. not all GPs).

It is possible to link the primary care practice records (CPRD) to secondary care data (HES) and cancer specific information (NCRAS) as well as death certification (ONS) for those patients who consent to the linkage scheme.

Semi-structured and unstructured local and regional data are also available through the NIHR Health Informatics Collaborative and NHS England's Local Health Care Record Exemplars (LHCREs). These include structured de-identified data within a common platform for the development of analytics with mapping against current standards from cancer tracking and reporting systems, prescribing systems and radiotherapy systems and EHRs and unstructured, de-identified data such as clinical letters and discharge summaries, laboratory test results, imaging and pathology reports through contemporary text and language processing tools.

Each of these data sources has both strengths and weaknesses. For example, the SACT database began data collection in 2012 and was mandated from April 2014, capturing those patients receiving systemic therapies in England. SACT represents a national, inclusive dataset containing data from over 600,000 patients treated in England (at time of publication), which allows patient-level linkage to other PHE-held datasets.

Whilst coverage is broad, there are some issues around completeness, particularly with respect to data in the outcome fields around final treatment, regimen changes and regimen outcome summary (see Data Completeness Reports published by SACT). It does, however, allow, for example, for analysis of 30-day mortality after chemotherapy for breast and lung cancer in a large cohort of patients.

SACT remains one of the most unique datasets in the world with huge potential for real-world data analytics. With respect to OBP schemes the data maturity allows survival studies of poor prognosis cancers but not yet of good prognosis populations (those with longer survival expectations). Moreover, the ability to link to real-world adverse events (particularly those that happen outside of hospitals) remains to be accomplished but should, in time, be possible.

National cancer audits, coupled with investments from Health Data Research UK and increased health systems research initiatives, like the Bowel Cancer Intelligence Centre (BCI UK) at Leeds University should support further improvements. Having a consistent definition of cancer progression and recurrence is key to supporting OBP schemes that are implementable and acceptable to all parties; definitions of these parameters currently vary between datasets.

Better linkage using proxy and indirect identifiers, better coding approaches and machine learning, and high-resolution validation studies also have the potential to increase the value of health and cancer care data in the UK, which could expand the possibilities of OBP schemes in the NHS.