FORUM
Academy of Medical Sciences

Looking to the future: oncology endpoints

Summary report of a joint workshop held on of 3 July 2017 by the Academy of Medical Sciences and the Association of the British Pharmaceutical Industry

The Academy of Medical Sciences

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The Academy of Medical Sciences

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The Academy of Medical Sciences' FORUM

The Academy's FORUM was established in 2003 to recognise the role of industry in medical research, and to catalyse connections across industry, academia and the NHS. Since then, a range of FORUM activities and events have brought together researchers, research funders and research users from across academia, industry, government, and the charity, healthcare and regulatory sectors. The FORUM network helps address our strategic challenge 'To harness our expertise and convening power to tackle the biggest scientific and health challenges and opportunities facing our society' as set in our Strategy 2017-21. We are grateful for the support provided by the members and are keen to encourage more organisations to take part. If you would like further information on the FORUM or becoming a member, please contact forum@acmedsci.ac.uk.

The Association of the British Pharmaceutical Industry

The ABPI represents innovative research-based biopharmaceutical companies, large, medium and small, leading an exciting new era of biosciences in the UK. Our industry, a major contributor to the economy of the UK, brings life-saving and life-enhancing medicines to patients. We represent companies supplying more than 80 per cent of all branded medicines used by the NHS, and are researching and developing the majority of the current medicines pipeline, ensuring that the UK remains at the forefront of helping patients prevent and overcome diseases. Globally, our industry is researching and developing more than 7,000 new medicines. The ABPI is recognised by government as the industry body negotiating on behalf of the branded pharmaceutical industry for statutory consultation requirements including the pricing scheme for medicines in the UK.

Opinions expressed in this report do not necessarily represent the views of all participants at the event, the Academy of Medical Sciences, or its Fellows.

All web references were accessed in August 2017.

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Preface

Despite many recent advances, cancer remains an area of great unmet medical need. This has created a strong drive to translate an increasingly detailed understanding of the mechanisms underlying cancer into safe and effective treatments as rapidly as possible. To facilitate access, there has been considerable innovation in areas such as therapy development and clinical trial design, including the use of new endpoints – the outcome measures used to assess the clinical efficacy of interventions.

The use of new, or different, endpoints offers the potential to accelerate the development of anti-cancer treatments but also raises challenges for groups such as regulatory agencies and those responsible for health technology assessment, reimbursement and commissioning. Choice of endpoint also needs to reflect the interests and priorities of other groups such as clinicians and patients, the ultimate beneficiaries of new interventions.

In recognition of their importance to multiple communities, on 3 July 2017 the Academy of Medical Sciences and the Association of the British Pharmaceutical Industry (ABPI) jointly hosted an interdisciplinary FORUM meeting on endpoint selection and novel endpoint development in oncology. The event brought together key stakeholders – including representatives from industry, academia and the legal sector, as well as regulators, clinicians and patients – to discuss the challenges associated with endpoint selection in oncology, and how to ensure that clinical trial outcome measures are fit-for-purpose in a rapidly evolving landscape.

This report provides a summary of the discussions and presentations from the workshop, including emergent themes and opportunities for further discussion. It should be noted that this document reflects the views expressed by participants at the meeting and does not represent the views of all participants or of the Academy of Medical Sciences or ABPI.

Executive Summary

Given the high levels of unmet need in cancer, there is a strong desire to see more rapid translation of new scientific knowledge – that is, faster and more efficient development of new interventions and better patient access to safe and efficacious products.

Selecting the correct endpoints is essential for assessing the efficacy and safety of therapies. However, a multitude of factors are presenting challenges to the use of 'traditional' endpoints and driving innovation in endpoint development and use. These factors include trends towards stratified medicine and smaller patient groups, novel forms of therapy, innovations in clinical trial design, and adaptive regulatory pathways and priority medicine schemes including accelerated assessment.

A key question, therefore, is what constitutes a meaningful endpoint in oncology, given the distinct needs of different stakeholder groups. Over the course of the day, workshop participants explored this challenge and how the different stakeholder groups could collectively work towards a framework, or principles, to guide the use of endpoints in clinical research.

Emerging themes

- **Overall survival has been the 'gold standard' endpoint in oncology trials to date, but it is increasingly apparent that this is not always well suited to emerging models of therapy development, clinical evaluation and patient preference.** Overall survival has provided the most objective and clear measure of survival benefit but the 'relevance' of this outcome, as well as the practicality of determining overall survival through large and lengthy randomised controlled trials, is being increasingly challenged.
- **Surrogate endpoints – developed on the premise of being predictive of overall survival – may overcome some of the practical issues of determining overall survival, but their association with survival may be unclear.** However, surrogate endpoints may also be a useful tool in the drive for accelerated assessment as they are more suited to rapid clinical evaluation. Each surrogate endpoint has its own strengths and limitations but the most appropriate endpoint for each different clinical trial may be unclear, particularly given the uncertainty around their validity as indicators of survival benefit.
- **Using meaningful endpoints which are relevant to regulators, payers, clinicians and patients requires measurement of factors beyond overall survival.** Overall survival is not the only meaningful outcome and other reliable endpoints are required to assess the impact of treatment from clinical and patient perspectives. Examples include impact on pain relief, symptom control and other aspects relating to quality of life. Treatments may deliver patient benefits in addition to, or instead of, increasing overall survival. From a patient's perspective, benefits need to be weighed against the risks and drawbacks of treatments including impact on quality of life and daily living; quality of life

may be at least as important, and potentially more so, than longevity. Impact on quality of life may be harder to capture than 'objective' measures of treatment responses, and there is a need for new standardised and validated tools to capture patient-reported outcomes.

- **It is increasingly difficult to apply 'one-size-fits-all' approaches to endpoint selection, which poses challenges to regulatory agencies and health technology assessment (HTA) bodies.** The diversification of potential endpoints and unique features of different cancers and different therapies are making it difficult to apply the same approaches across all situations. What is appropriate for one type of cancer, or stage of disease, may not be suitable for another. Regulatory agencies have traditionally based decisions on overall survival, but have shown a willingness to consider alternative endpoints, particularly in accelerated assessment, and to adopt a case-by-case approach. HTA organisations also typically model long-term survival benefits using trial data such as overall survival. However, with advances in the use of different measures, these analyses can be hampered by a lack of data on overall survival and uncertainties about the association between surrogate endpoints and overall survival. As new endpoints are introduced, consistency across regulatory and HTA bodies internationally is highly desirable.
- **More research is needed to validate surrogate endpoints and novel biomarkers, including their association with patient benefits.** To provide confidence in existing surrogate endpoints and novel outcome measures emerging from laboratory research, more work is needed to clarify their association with overall survival or other patient benefits. To support appropriate choice of endpoints, this validation needs to be tailored to different diseases, stages of disease, types of therapy and patient groups.
- **Electronic health records and other forms of real-world data offer new opportunities for endpoint development and validation.** Clinical data from medical records and other data registries could be used as the basis of new endpoints. In addition, routine data could be used in long-term tracking of patient responses and endpoint validation.
- **There is a continuing need for multi-stakeholder dialogue.** It is important for all parties to recognise the need for flexibility and to engage in multi-stakeholder dialogue. Early and regular contact between industry and regulators will be essential, as will integrating patient communities into research design and delivery as well as conversations about endpoint selection.
- **The lessons learned from cancer are likely to be relevant to other fields of medicine.** Although many endpoint selection issues are specific to cancer, general principles are also likely to be relevant to other fields of medicine, such as treatment of rare diseases, preventive treatment of late-onset conditions and curative gene therapy. Similarly, experience in these fields could inform developments in oncology.
- **The field of regulatory science will help to consider challenges around endpoints and other critical questions.** Regulatory science – the use of scientific methodologies to support regulatory assessment and decision-making – is an emerging discipline with the potential to enhance regulatory decision-making processes. The UK's existing strengths in this area could be further recognised to enable it to play a leading role internationally and to help ensure regulatory processes are fit-for-purpose.

Introduction

One in two people will develop cancer at some point in their lives, and more than 150,000 people die of the disease every year in the UK. Hence, despite much recent progress, there remains an urgent need for new and improved cancer treatment and management.

Rapid scientific progress is providing new insight into cancer biology, underpinning new treatments targeting specific molecular lesions in cancer cells and the emergence of stratified medicine, and reinvigorating fields such as immuno-oncology and cell-based therapies. These trends are driving considerable innovation in therapy development and clinical trial design, to accelerate the introduction of new therapies into the clinic and improve the efficiency of therapy development.

Scientific developments have been matched by innovation in the regulatory domain, with the introduction of various models for accelerated access. So-called 'adaptive pathways' have been established to ensure that patients benefit more rapidly from medicines of potentially major impact. In many cases, this involves some form of provisional ('conditional') licensing based on preliminary clinical evidence followed by re-evaluation as post-licensing data on the benefits and risks of treatment are generated by additional trials and through routine use of a treatment.

Endpoints are integral to clinical trial design, providing predefined outcome measures linked to patient benefit. The gold standard endpoint in clinical oncology has traditionally been overall survival, which provides the clearest indication that an intervention is benefiting patient survival. However, use of overall survival as an outcome measure has considerable drawbacks, not least the need for large and lengthy randomised controlled trials in many clinical settings. As a result, multiple surrogate endpoints have been developed (see Glossary), which provide alternative outcome measures that are likely to be predictive of overall survival but can be assessed over shorter timeframes.

Endpoints are also required to provide a rigorous assessment of the impact of interventions on the patient experience. This can span areas such as pain relief and symptom control, as well as more general impacts on quality of life and daily living. Commonly, these outcomes are reported directly by patients themselves. Each endpoint has its own strengths and weaknesses, and there has been considerable discussion about which are the most appropriate to use and under which circumstances. Of particular importance is the acceptability of particular endpoints to regulatory authorities, which draw on endpoint data in their risk–benefit analyses and decisions on the safety and efficacy of interventions.

The FORUM meeting provided an opportunity for stakeholder groups – including academics, clinicians, industry, regulatory authorities and patients – to come together to discuss the challenges of endpoint selection and development and ways to ensure that endpoints meet the needs of all communities. Annex 1 provides a summary of the meeting's formal presentations and the following sections summarise key themes emerging from panel discussions and breakout sessions.

Glossary

Endpoint: An outcome measured in a clinical trial, providing a quantitative assessment of the clinical impact of an intervention. In oncology, endpoints generally relate to patient survival.

Overall survival (OS): Period between randomisation in a trial and death from any cause; generally regarded as the 'gold standard' of oncology endpoints.

Surrogate endpoint: An endpoint that is not itself a direct measure of patient survival but is predictive of survival, and should capture the impact of treatment in the same way as a 'true' endpoint; can provide a more rapid and specific indication of the efficacy of a therapy.

Progression-free survival (PFS): Period between randomisation in a trial and disease progression (worsening of disease) or death.

Time to progression (TTP): Period between randomisation in a trial and disease progression.

Disease-free survival (DFS): Period between randomisation in a trial and the recurrence of a tumour or death.

Objective response rate (ORR): Proportion of patients with a reduction in tumour size by a pre-specified amount.

Time to treatment failure (TTF): Time between randomisation in a trial and stopping of treatment for any reason (e.g. disease progression, death or toxicity of treatment).

Duration of response (DoR): Period between documentation of tumour response and disease progression.

Minimal residual disease (MRD): Use of highly sensitive techniques to identify cancer cells present at very low levels.

Patient-reported outcome measure (PROM): An impact measure of the benefits or negative consequences of treatment reported directly by patients.

Health-related quality of life (HR-QOL): A measure of how well patients feel and function.

EQ-5D: EuroQol five dimensions questionnaire, a commonly used (but often criticised) tool for assessing HR-QOL.

Biomarker: A measurable and objective indicator of the presence or severity of a condition, or of an important trait of a condition; can provide convenient tools for monitoring and assessing the impact of treatment.

Discussion

1. Moving beyond overall survival

Discussions repeatedly emphasised the major challenges facing a highly dynamic field in which conventional approaches to drug development and clinical assessment are rapidly being superseded. Innovations in the types of therapies being developed, such as immunotherapies, the increasing focus on targeted drugs for specific patient subpopulations, and the need to evaluate wider benefits such as delayed development of drug resistance all have the potential to shape endpoint selection.

On the other hand, endpoints also need to be acceptable to regulatory authorities, which have traditionally relied on overall survival as the gold standard. As well as its advantage as a direct measure of survival, it also enables comparisons across different treatments. Overall survival is also the most commonly used metric for HTA analyses.

Although surrogate endpoints have great potential for accelerating the clinical development of therapies, their use was felt to present a range of challenges for regulatory authorities – particularly because of uncertainties surrounding their association with survival benefit. While regulatory decisions have been made on the basis of outcome measures such as progression-free survival, the relationship of surrogate endpoints with overall survival may not always be clear and may vary between diseases.

In some cases, it was suggested that enhanced progression-free survival might not lead to any benefits in overall survival. In the worst-case scenarios, treatment side effects could actually lead to increased patient harm and a reduction in overall survival despite enhanced progression-free survival.

Discussions therefore highlighted an underlying tension in clinical evaluation of oncology interventions. Overall survival may be the most reliable indicator of survival benefits, but may require lengthy trials and is therefore not well suited to the drive towards accelerated assessment; surrogate endpoints can give a faster readout, supporting accelerated assessment, but their ability to accurately predict survival benefits may be open to question.

2. Endpoints related to quality of life

Interventions may deliver additional patient benefits beyond survival, but may also have a detrimental impact on quality of life. Hence, as well as survival, endpoints are also required to assess other patient-centred outcomes, such as pain relief, symptom control and other aspects of quality of life. However, these outcomes are generally more subjective than biomedical responses; it can be challenging to collect reliable data on quality of life impacts, while a lack of standardised tools makes it difficult to draw comparisons across studies.

Participants repeatedly emphasised the need to gather more patient-reported outcomes. It was strongly felt that, for many patients, quality of life was at least as important – and often more important – than gains in longevity. This principle was not felt to be having the

influence it should on the clinical assessment of therapies. It was suggested that clinical trials were often not consistently gathering such information, leading to a paucity of data to feed into regulatory decision-making. Currently, quality of life endpoints tend to be supplementary to survival endpoints and surrogate endpoints of survival, rather than primary endpoints in their own right. Quality of life issues are of particular significance when the impacts of treatments on survival are small.

It was noted that, while patient-oriented outcomes should be central to NICE decision-making, it was currently hard to capture such outcomes robustly, consistently and quantitatively. It was felt that, as far as possible, outcome measures needed to reflect the unfiltered views of patients, although it was also recognised that some degree of standardisation would be required to facilitate data integration and analysis across trials.

In particular, it was felt that toxicity impacts on general wellbeing and daily lives were not captured well. Trials often gathered data on specific types of adverse event, but were less likely to consider more general quality of life issues. Tools commonly used to collect quality of life data, such as the EQ-5D survey, were not felt to be sensitive measures of factors important to cancer patients, although EQ-5D has the advantage of capturing data in a standardised format and is generalisable across disease areas.

It was suggested that patient-reported outcomes needed to be tailored to different types of cancers, which raises different quality of life issues. However, while a one-size-fits-all approach was not felt to be appropriate, it was also recognised that a proliferation of highly disease-specific approaches would also present practical challenges. Work would be needed to develop and validate novel patient-reported outcome measures, and it was important that this was done in conjunction with the regulatory and HTA communities to ensure that data were compatible with decision-making processes. Clinical researchers are also needed to examine patient-related outcomes specific to a study as well as general quality of life data.

It was also emphasised that bodies such as NICE have discretion to consider quality of life factors in addition to input from evidence review groups (and submissions from other stakeholders). Indeed, recommendations have been overturned by appraisal committees on the basis of quality of life concerns. It was also stressed that the goal of economic analyses is to integrate a wide range of factors, including quality of life as well as clinical effectiveness and cost, but such analyses are dependent on the availability of suitable patient-reported outcome data.

New opportunities for data collection and patient engagement

The explosive growth of smartphone apps and other new technologies were felt to be opening up a wealth of new opportunities for collecting data from patients, but major challenges existed in aggregating and integrating such data and establishing validated outcome measures that could be widely adopted.

Some participants also raised concern about the potential for over-collection of data from patients. It was suggested that, given the time and effort involved, patients should only be asked to contribute data when there was a realistic likelihood that information would actually be used.

Participants also suggested that the pharmaceutical industry as a whole was seeking to engage with patients more along the entire drug development pathway, with full involvement in research design and delivery, to ensure that products better meet their needs.

Supporting informed patient–clinician dialogue

It was argued that a lack of data on the impacts of cancer treatments on quality of life may result in patients having unrealistic expectations of anti-cancer treatments. If additional patient-reported outcome data were available, clinicians and patients could have more informed discussions about the benefits, risks and likely impact of treatments on daily living, as part of joint decision-making processes.

For example, participants discussed a study examining patients' experience of drugs introduced on the basis of progression-free survival data. It found that clinicians were often prescribing drugs on the basis of little evidence, instead of considering a shift to palliative care. This work also revealed that quality of life was considered extremely important by patients, whose attitudes were shaped not only by the prospect of longer survival but also by the impact of treatment on daily living. It was suggested that clinicians might be placing too great an emphasis on survival without enough consideration of the wider impact of treatment on patients.

3. A diversity of tailored approaches

Attendees expressed a desire to make more use of novel endpoints that are better suited to new models of research and development and clinical assessment. However, this was tempered by a recognition that these novel endpoints needed to be endorsed by regulatory authorities, and underpinned by robust methodologies and a deep understanding of their biological and clinical relevance.

Due to the diversification of potential endpoints, introduction of innovative trial designs and use of novel interventions, participants suggested that it was increasingly difficult to apply the same approaches across all conditions. What is appropriate for one type of cancer, stage of disease, or type of therapy may not be suitable for another. Hence, it was felt that regulatory decision-making needed to move beyond 'one-size-fits-all' approaches to endpoint selection, to take account of the specific circumstances of different types of cancer and different types of treatment, and the specifics of different diseases more generally.

Participants suggested that, given their key role and influence on endpoint selection, regulatory agencies needed to adopt more flexible approaches in light of the changing nature of cancer therapy development. Indeed, it was acknowledged that, contrary to some perceptions, regulators are showing flexibility in the light of rapidly changing circumstances, although they may not necessarily have the tools to be able to make use of certain endpoints.

Representatives of regulatory agencies emphasised the importance of adopting a case-by-case approach. Potentially, some general principles of appropriate endpoint selection could be developed and tailored to the specific circumstances of individual conditions.

In certain areas, such as use of historical controls, some participants felt that there was currently insufficient guidance from regulators. It was also suggested that there was currently no framework for evaluating the acceptability of emerging biomarkers from a regulatory perspective.

Participants also highlighted the potential legal implications of regulatory decision-making based on limited surrogate endpoint data. Should drugs turn out to have long-term negative consequences, patients might be inclined to seek legal redress, potentially targeting regulators as well as companies. It was suggested that there might be a need to examine

legal risk-sharing between regulators and companies for drugs following accelerated approval pathways.

Modelling long-term benefits

Uncertainty surrounding the likely clinical benefits of an intervention was acknowledged to be a particular challenge for HTA organisations and bodies such as NICE, which often have to model potential long-term impact – particularly on overall survival – on the basis of limited data. Traditionally, these analyses have drawn primarily on overall survival data from randomised controlled trials.

As more data are gathered on the clinical impact of an intervention, the relationship between surrogate endpoints and overall survival may change. In addition, as diseases evolve (for example, by acquiring drug resistance), the significance of surrogate endpoints may also change. This fluidity could affect HTA analyses, which may be one reason why HTA bodies are often reluctant to use such measures.

In some cases, NICE has based incorporated analysis of progression-free survival data in its decision-making, following a rigorous analysis of their relationship with overall survival and the impact of different strengths of association. The need was emphasised for clarity on the assumptions made when using surrogate endpoints such as progression-free survival and for supporting evidence to justify such assumptions.

Developing globally consistent approaches

Participants highlighted the value of aligning licensing and HTA activities, ideally internationally, although it was acknowledged this was challenging in practice. Nevertheless, it was suggested that steps could be taken to build methodological consensus and development of shared practice across these domains.

It was noted that some progress had been made in Europe to coordinate regulatory and HTA input, as part of the PRIME early access initiative. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) was suggested as a possible mechanism for achieving greater international consistency.

4. The need for more validation research on surrogate endpoints and novel biomarkers

Given current uncertainties, particularly surrounding the associations between surrogate endpoints and overall survival, as well as the emergence of new biomarkers, participants identified a need for more work to validate novel endpoints. Cultural shifts might also be needed, for example in academia and industry, to encourage wider use of unconventional endpoints.

Development and use of novel endpoints was felt to go hand in hand with innovative trial design. A general trend towards targeted therapies and smaller patient subpopulations emphasises the importance of careful patient selection, fully understanding an intervention's mechanism of action, and developing an appropriate trial design, all of which could influence choice of endpoint.

Implications of adaptive pathways

It was suggested that there was a need to think more broadly and consider 'accelerated progress' rather than just accelerated approval, and to speed up all stages of translation. Emerging biomarkers of potential value as endpoints could be of particular value in adaptive trials, which require rapidly assessable endpoints so that decisions can be made in reasonable timeframes. Participants emphasised the need to ensure that biomarkers tracked features that were relevant to patients.

For therapies approved through accelerated access pathways, efficient collection and analysis of real-world patient data were recognised to be essential, albeit challenging, and would provide key data for endpoint validation.

Emerging opportunities for biomarker and endpoint development

Laboratory research and a deeper understanding of the mechanisms of cancer are generating a wealth of new opportunities for biomarker and endpoint development. Again, it was noted that it was important to consider not just the utility of such biomarkers in research but also their relevance to patient benefits.

In particular, clinical trial design requires in-depth consideration of the clinical aim of an intervention, how this can best be assessed and by which endpoint. Patients have an important role to play in ensuring that the measures reported are meaningful to those affected.

Imaging was felt to be a technology of particular value as a source of new endpoints and as a way of measuring endpoints. For example, imaging enables responses to therapy to be tracked over time. However, a significant challenge to the use of imaging biomarkers is fully understanding the relationship between observed responses and patient benefits. Imaging may also depend on the implementation of complex technology requiring specialist skills.

Exploiting deep biological data

Techniques such as liquid biopsies and 'omics' technologies were felt to offer opportunities to acquire much deeper biological data, across all stages of drug development and clinical assessment. As well as their potential practical value as biomarkers or trial endpoints, such data could also provide deeper mechanistic insight into reasons behind the success or failure of interventions.

It was suggested that sample collection could be integrated into all trials, to create long-term biological resources for improving understanding of cancer biology and validating biomarkers. The use of different types of biomarkers, for example those predicting relapse or identifying subclinical disease, might also require sensitive discussions with patients about the meaning of results and their implications for individuals. It was also suggested that existing data could be analysed to identify additional markers associated with survival (or quality of life), to inform the development of novel endpoints.

5. Exploiting big data opportunities

Evidence from real-world use of interventions was felt to offer significant opportunities for endpoint development and validation, but major challenges would need to be addressed.

Classification systems used in electronic health records and other data registries could provide the foundation of novel endpoints, but considerable work would be needed to develop useful and reliable outcome measures compatible across different data platforms.

Routinely collected data could provide additional evidence for validating novel biomarkers. Clinical records also provide a potentially rich source of data on the long-term impacts of interventions, spanning benefits and risks, supplementing and extending data collected in the context of clinical trials. It was felt that more work was required to develop systems for collecting and analysing routine data of high enough quality to support regulatory and clinical decision-making. Nevertheless, this approach has the potential to offer a flexible and cost-effective complement to traditional randomised controlled trials.

The Salford Lung Study was identified as an initiative where mechanisms had been established to obtain reliable data from routine clinical practice (but at considerable cost). The need for high-quality data entry was seen to be critical, raising questions of whose responsibility this should be and whether an NHS-wide initiative was needed to enhance routine data collection practices.

6. Encouraging multi-stakeholder dialogue

Given the current pace of scientific development and uncertainties around the full validity and utility of, and association between, some endpoints, early and regular dialogue between stakeholder communities was felt to be essential. It was suggested that paths to the future should be shaped through close and regular interactions between all communities, including patients.

Participants identified a range of ways in which information can be exchanged between stakeholder groups. Pipeline meetings were suggested as one route through which industry and regulators can discuss clinical evaluation issues early in the life cycle of therapies. Publications such as concept papers and position papers from regulators can provide a relatively rapid mechanism to provide insight into regulators' thinking and stimulate discussion, as formal guidance documentation inevitably takes longer to agree and publish.

7. Sharing learnings across fields of medicine

Oncology is in the forefront of innovation in trial design and clinical evaluation of new interventions. Although many issues raised by the use of novel endpoints are specific to cancer, general principles are also likely to be relevant to other fields of medicine. In particular, selection of appropriate endpoints is likely to be similarly challenging in areas such as treatment of rare diseases, preventive treatment of late-onset conditions and curative gene therapy, where lessons learned in oncology could be highly relevant. Similarly, experience in these fields could inform developments in oncology.

8. Promoting regulatory science

The current uncertainty and many unanswered questions highlight the potential role that could be played by regulatory science in developing an evidence base to guide future practice. Regulatory science – in this case the use of scientific methodologies to support regulatory assessment and decision-making – was felt to be relatively well developed within the USA but had yet to become fully recognised in the UK. Nevertheless, there was thought to be a sufficient foundation to enable the UK to take a leading role in the development of the field.

Conclusion

The field of oncology is undergoing rapid change. While great progress has been made in many areas, there is still an urgent need to accelerate the development of new treatments. On the other hand, a deeper understanding of cancer and new technologies are generating new opportunities, particularly for medicines targeting specific molecular defects in cancer cells and for novel cell-based therapies. Innovative trial designs are being developed to take account of these emerging paradigms and to accelerate the clinical assessment of therapies. Adaptive pathways have been introduced to ensure patients benefit more rapidly from potentially game-changing new medicines.

All of these developments have significant implications for choice of endpoint in clinical trials. Overall survival has long been the gold standard of cancer trials, but is increasingly problematic to apply in smaller, shorter trials. A wide range of biomarkers and surrogate endpoints are being introduced or are in development, but the uncertainty surrounding their association with overall survival raises significant issues, particularly for regulatory agencies and HTA organisations. Furthermore, patient-centred endpoints assessing impacts on quality of life may not yet be receiving the emphasis they merit.

The FORUM meeting provided an opportunity to air these challenging issues. Innovative endpoints are likely to be critical to the accelerated development of new medicines, yet their introduction will have significant implications for multiple communities. During this period of uncertainty, an important overarching theme was the need to continue multi-stakeholder dialogue, as progress will be most swift, and patients will benefit most rapidly, if the activities of all parties are aligned. Such discussions should include patients, and recognise the need to capture more comprehensively not just survival benefits but the impact of interventions on patients' daily lives.

Furthermore, while oncology is in the forefront of changing practice, it is facing challenges that will be shared with other fields of medicine. While some issues may be specific to cancer, many of the general principles discussed are likely to be of wider relevance, and there will be important opportunities to learn lessons from cancer that can be applied to innovative therapy development in other areas of medicine.

Annex 1: A summary of meeting presentations

Establishing endpoints for clinical design and regulatory approval

Professor Sir Michael Rawlins, GBE (Knight Grand Cross) FMedSci, Chair of the Medicines and Healthcare Products Regulatory Agency (MHRA), emphasised that it was a timely moment to be discussing endpoints in cancer. Driven by the urgent need to reduce the time taken for new medicines to reach patients and to capitalise on emerging scientific opportunities, the clinical assessment of interventions is undergoing considerable change. New trial designs are being introduced – including adaptive trials, umbrella and basket trials and Mendelian randomisation studies – which require thought on the most appropriate endpoint and are driving the development of novel endpoints.

In addition, therapies are increasingly used in novel combinations, again requiring consideration of choice of endpoints. Surrogate endpoints can also function as biomarkers, providing new opportunities for clinicians to monitor the progress of patients and modify treatment plans according to patient response.

Professor Rawlins argued that it is important for all stakeholder groups – academics, clinicians, industry, regulatory bodies, those responsible for health technology assessments and patients – to consider these issues collectively. Academic research can identify new biomarkers that may hold potential as proxies of clinical outcome measures; industry may need to adopt innovative measures in clinical assessment; regulators need to be open to validated new outcome measures; and patients have a key role in ensuring that endpoints reflect outcomes that are important to them. An overarching message was that endpoints needed to reflect direct patient benefit and outcomes considered desirable from a patient perspective.

Global trends and principles for endpoints

Regulatory authorities use endpoint data as the basis of their benefit–risk analyses. They have considerable influence on the selection of endpoints in clinical trials – the endpoints that regulatory authorities consider informative and necessary for the purposes of licensing decision-making will have a significant impact on the choice of endpoints by those organising trials.

Dr Lorraine Pelosof, Medical Officer at the US Food and Drug Administration (FDA), discussed the FDA perspective on endpoints. She pointed out that the remit of the FDA relates to the safety, efficacy and security of drugs and devices; it does not consider cost/reimbursement issues or assess clinician practices.

Dr Pelosof emphasised the critical role of endpoints for the assessment of efficacy. Ideally, they provide a direct measure of clinical benefit. Overall survival – the traditional gold standard – provides the clearest indication of survival benefit, but as death is the final point in the natural trajectory of disease, trials generally need to be long and large to demonstrate an impact on overall survival. Measurement of overall survival also requires a conventional randomised controlled trial and is confounded by cross-over and subsequent therapies – significant issues for trials of targeted therapies with small numbers of patients.

Other clinical outcome measures can be used to provide data on signs and symptoms of disease, including measures recorded directly from patients ('patient-reported outcomes'). These have the advantage of relating directly to the patient's experience, but it can be challenging to assess objectively how patients feel and function and to determine what represents a successful response.

Dr Pelosof emphasised the distinction between 'true' endpoints – which provide a direct measure of clinical benefit – and surrogate endpoints, which are intended to be predictive of clinical responses. Multiple surrogate markers have been developed (see Glossary). Radiographic approaches, for example, can be used to assess the impact of treatment on tumours. Information can be gathered much more rapidly through such approaches but there is inevitably some degree of uncertainty about how the observed effect on a tumour translates to a clinical benefit.

Other surrogate markers are used in specific situations, and the FDA has shown a willingness to embrace novel endpoints. For example, pathological complete response – complete removal of tumour cells in breast cancer before surgery – has been used in licensing of breast cancer treatments, while immune endpoints are in development for immunotherapies. Several haematologic endpoints have been proposed for haematological malignancies.

Accelerated versus regular approval

Surrogate markers play a particularly prominent role in accelerated approval processes, for therapies addressing serious conditions that lack effective treatments. Objective response rate is often used as a surrogate endpoint in accelerated approval decision-making, with the expectation that a larger confirmatory trial will be undertaken with endpoints assessing direct clinical benefit (or with well-established surrogate endpoints, depending on the specific condition).

Consistency of approach

Dr Pelosof noted that both the FDA and the European Medicines Agency (EMA) were willing to consider alternative endpoints such as objective response rate measures (under appropriate circumstances). The FDA has monthly teleconferences with regulatory authorities in Europe, Canada, Japan and Australia to share experience and coordinate activities.

One overarching message was that the selection of endpoints is highly context-dependent – the most appropriate endpoint is dependent on the specific condition, stage of disease, patient population, trial design and understanding of underlying biology. Dr Pelosof recommended early and regular contact with regulatory agencies to discuss choice of endpoint.

Using electronic health records for endpoints

Clinical trials generate high-quality data on the impact of treatments but are expensive and time-consuming. A possible complementary approach, discussed by Professor Harry Hemingway, Director of the Farr Institute London, is to capitalise on data held in electronic health records (EHRs).

Although not as high quality as trial data, EHR data could be a highly cost-effective source of evidence providing insight into both safety and efficacy. They also provide an opportunity for long-term data collection across all aspects of health, not just those assessed in trials. Furthermore, Professor Hemingway identified several possible applications of EHRs, including capture of data during trials, informing trial design and endpoint selection, optimising endpoint specifications and providing a source of real-word evidence for long-term assessments and health economic evaluations.

Drawing on his long experience in cardiovascular medicine, Professor Hemingway provided reassuring evidence that endpoint data extracted from EHRs can be highly consistent with those obtained during trials.[1]

From data to endpoint

In cancer, a multiplicity of data sources could be used for endpoint development (although significant gaps include patient-reported measures and primary care). However, exploiting these resources to generate endpoints that are reliable and meaningful to regulators is likely to be highly challenging.

Relevant information may exist in codes used for diseases/symptoms and also for procedures; however, different sources may use different coding systems. In addition, imaging data may be hard to integrate into endpoints. Overall, although the experience of cardiovascular medicine suggests that usable endpoints could be extracted from electronic data sources, it would require significant amounts of work. There would also be a need to ensure consistency between countries.

On the other hand, data extraction could provide additional valuable information, for example generating an unbiased view of pathways of disease progression. Detailed data may also suggest specific clinical manifestations that should be monitored in trials.

Summing up, Professor Hemingway argued that realising the potential of EHR data in oncology would require a top-down, coordinated and international approach. He identified the Innovative Medicines Initiative (IMI) Big Data for Better Outcomes programme as a possible starting point, and Health Data Research UK as a national health data science initiative that could be challenged to take forward this kind of work.

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[1] West of Scotland Coronary Prevention Study Group (1995). *Computerised record linkage: compared with traditional patient follow-up methods in clinical trials and illustrated in a prospective epidemiological study.* J Clin Epidemiol. **48(12)**, 1441–1452.

Endpoints of relevance to patients

Presenting the patient point of view, Simon Denegri, Chair of INVOLVE, suggested that trial endpoints and other treatment outcome measures had to date paid too little attention to patients. The efficacy of treatments is generally framed in terms of quantitative gains in survival, yet patients also need to balance these gains against detrimental impacts on quality of life. Quoting Dr Alice Biggane in Liverpool, Mr Denegri suggested that: "doctors know about the illness but patients know about the impact".

As a result of this neglect of the patient perspective, trials may not gather evidence on impacts that matter to patients. Patients may therefore begin treatment not fully aware of its likely impact on their daily lives, or having expectations that are not matched by reality.

Hearing the patient voice

Potential ways forward could include greater patient involvement in trial design and endpoint specification. There is also a need for a core set of outcome measures that could be widely adopted to provide consistent data sets, as being developed by the COMET (Core Outcome Measures in Effectiveness Trials) initiative.[2]

Greater use of real-world evidence could increase the amount of information available on the long-term impact of treatments on patients. In addition, new technologies, particularly smartphone apps, greatly increase the potential for patients to capture and share data. Longer-term follow-up of patients after trials could also help to generate a more complete picture of the impact of treatments.

Mr Denegri concluded by highlighting the challenges in communicating medical evidence to general audiences, and suggested that informal sources of information such as family and friends, as well as the media, were highly influential. Many people may hold a simplistic 'cause or cure' view of medicine, with unrealistic expectations of what therapies can achieve in oncology.

Clinical validity of endpoints: the oncologist's view

Professor Mark Emberton FMedSci, Professor of Interventional Oncology and Honorary Consultant Urological Surgeon at University College London, highlighted some of the practical challenges that cancer researchers face when selecting suitable trial endpoints, focusing on his specialty, prostate cancer.

Prostate cancer presents a unique set of challenges. It is common, but as it typically appears in later life, it is not necessarily associated with premature mortality and so treatment may not be necessary (clinicians opting instead for 'active surveillance'). Levels of prostate-specific antigen (PSA) can provide an early warning sign of prostate cancer but are not a strong indicator of clinically significant disease and may change for clinically unimportant reasons. In addition, surgical treatment has a significant risk of side effects on urinary and sexual functions. Hence there is a need for improved methods of both diagnosis and treatment.

[2] www.comet-initiative.org

Professor Emberton discussed two prostate cancer case studies – use of an imaging technology to improve patient stratification and reduce the need for invasive biopsies, and a trial of a tissue-sparing treatment technology (see Boxes).

These examples illustrate how innovative studies often require the development of novel endpoints. Discussions with patients and regulators are an important aspect of this development, and trials likely to form part of submissions to regulatory agencies are particularly challenging.

The PROMIS prostate cancer imaging trial

The PROMIS trial examined whether magnetic resonance imaging (MRI) could be used to triage patients with elevated PSA levels, to reduce the numbers of patients undergoing intrusive biopsies. A reference test was devised, based on biopsies taken at 5 mm intervals across the prostate, which was compared with the standard diagnostic technique – ultrasound-guided biopsy – and MRI.

One of the trial's key challenges was to define 'clinically significant' cancer. A measure was developed based on the tumour grading system used in prostate cancer and the size of tumour detected.

The trial found that triaging patients using MRI would allow 27% of patients to avoid a biopsy, reduce the numbers of clinically insignificant tumours detected, and increase the numbers of clinically significant tumours identified.[3] Despite these positive findings, the approach has yet to be endorsed by NICE, in part because of the technical challenges involved in this use of MRI.

Photodynamic therapy

An international multicentre trial compared a tissue-sparing photodynamic therapy with active surveillance in a low-risk cohort of patients. It found that the photodynamic therapy was safe and effective, with low levels of reported side effects on urinary and sexual function.[4]

The study required extensive interaction with regulators on trial design and endpoint selection. Notably, primary endpoints developed in discussion with regulators related to cancer progression, yet a strong motivator for the study

[3] Ahmed HU, *et al*. (2017). *Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study.* Lancet. **389(10071)**, 815–822.
[4] Azzouzi AR, *et al*. (2017). *Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial.* Lancet Oncol. **18(2)**, 181–191.

(and of particular importance to patients) was the desire to minimise the impairments of urinary and sexual function commonly seen with more radical surgery.

Health technology assessment of surrogate endpoints

The purpose of health technology assessment (HTA), suggested Dr Nick Latimer, Senior Research Fellow at the University of Sheffield, is to support the rational allocation of scarce healthcare resources. In essence, this is based on a quantitative analysis of the benefits of a new intervention – generally expressed in terms of quality-adjusted life years gained – and its incremental cost, to give an indication of likely cost-effectiveness.

HTA bodies rely on economic modelling, drawing on whatever clinical data are available. In oncology, modelling typically considers three health states – 'progression-free', 'progressed' and 'dead'. Techniques such as partitioned survival analysis are used to model the future survival of patients based on available clinical trial data, to provide an estimate of long-term clinical benefits.[5] An alternative approach, state transition models, attempts to model transitions between the different health states.

Use of surrogates

For models that include health states for 'PFS' and 'OS', HTA analyses generally use statistical models fitted to the progression-free survival and overall survival data observed in the relevant clinical trial to estimate the time spent in each health state: data on progression-free survival are used to estimate PFS, and data on overall survival are used to estimate OS. Surrogate endpoints are not usually used to estimate OS. Under some circumstances, however, particularly when such data are sparse, surrogate endpoints such as progression-free survival have been used in the estimation of OS, although there is concern about their reliability as a predictor of overall survival.

In some cases, NICE has accepted the use of progression-free survival data, particularly when evidence review groups have thoroughly analysed its relationship with overall survival and included sensitivity analyses exploring the impact of different strengths of association. When such analyses have not been carried out, NICE committees have been less inclined to be influenced by surrogate endpoint data.

In its guidance notes, NICE stresses that it regards clinical endpoints as more informative than surrogate endpoints but is willing to consider surrogate data as long as evidence is provided to support the association between surrogate and clinical endpoint.[6] The utility of surrogate endpoints is ultimately dependent on the extent to which they can predict health-related quality of life and/or survival, and NICE also recommends that uncertainty in this

[5] Woods B, *et al.* (2017). NICE Technical Support Document 19:Partitioned survival analysis for decision modelling in health care: A critical review, Report by the Decision Support Unit.
[6] NICE (2013) Guide to the Methods of Technology Appraisal.

association is acknowledged and analysed quantitatively.

Accelerated access in the UK

Professor Richard Barker OBE, Director of the Centre for Sustainable Medical Innovation (CASMI), discussed the potential implications of accelerated access schemes in the UK. In 2016, the Accelerated Access Review made a series of recommendations to accelerate the introduction of innovative new medicines.[7] At the heart of its proposals was an approach that would enable treatments of potentially major impact on patients to be awarded conditional approval status and made available to patients, followed by a period of post-approval data collection on safety and efficacy during real-world use.

Accelerated access is also a key aim of the MHRA's Early Access to Medicines Scheme (EAMS) while the FDA in the USA and EMA in the EU (the PRIME initiative) have also established accelerated approval mechanisms. The IMI's ADAPT-SMART project is also investigating conceptual frameworks that could support adaptive licensing pathways.[8]

Professor Barker suggested that these 'adaptive pathways' should form part of a more general 'adaptive mindset' emphasising flexibility and innovation in methods of drug development, assessment and evaluation of effectiveness.

Nevertheless, adaptive pathways can present challenges. Accelerated approval processes are designed for medicines having a significant beneficial impact. However, if intermediate analyses suggest a drug is highly beneficial, trials may be halted for ethical reasons, making overall survival and progression-free survival analyses difficult to perform. Furthermore, new mechanisms such as drug registries will be needed to collect data on drug use, raising questions about payment for data collection and the responsibilities of patients to contribute to data collection.

Professor Barker suggested that public and patient involvement had been pivotal to the work of the Accelerated Access Review and should continue to be important as new regulatory mechanisms were developed and piloted.

He noted that development and validation of biomarkers would continue be critical in understanding and treating cancer. Moreover, he also highlighted the fact that other fields of medicine would face similar and additional endpoint-related challenges, including treatment of rare diseases, one-off gene therapy applications, anti-ageing therapies and presymptomatic treatment of conditions such as Alzheimer's disease.

Access challenges associated with different endpoints

Regulatory authorities have shown a willingness to consider alternative endpoints, but in practice advisory groups may be reluctant to rely on surrogate endpoint evidence. Tania Krivasi, Group Health Economics Manager at Roche, discussed a case in point, related to the

[7] Department of Health (2016). Accelerated Access Review: Final Report. https://www.gov.uk/government/publications/accelerated-access-review-final-report
[8] http://adaptsmart.eu

neoadjuvant treatment of breast cancer with pertuzumab (Perjeta).

The impact of neoadjuvant treatment, pretreatment of breast cancer with drugs in advance of surgery, can be assessed through a measure known as 'pathological complete response' (pCR) – in effect, the absence of tumour cells on histological examination. This can provide a very rapid evaluation of treatment efficacy.

Since survival times for breast cancer treatments have improved, obtaining data on overall survival requires long-term trials with large numbers of patients. Nevertheless, there are still aggressive forms of breast cancer where new treatments are urgently needed. In recognition of this significant unmet need, both the FDA and EMA have recognised the potential importance of rapid surrogate endpoints such as pCR.[9,10]

Attempts have been made to assess the association between pCR and long-term benefits such as event-free survival and overall survival. The Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) group, established by the FDA, carried out a meta-analysis of 12 trials of neoadjuvant treatment of breast cancer, covering nearly 12,000 patients.[11] A pooled responder analysis showed clear benefits of pCR in terms of event-free survival and overall survival. On the other hand, analysis of individual trials found no correlation between the degree of pCR achieved and event-free survival and overall survival (possibly because of the heterogeneity of tumour types and low rates of pCR achieved in the trials).

Because of this uncertainty, NICE initially came to a negative conclusion about pertuzumab neoadjuvant treatment. However, a subsequent NICE appraisal committee approved the treatment, with clinical experts arguing in favour of the use of pCR on the basis that, despite the uncertainty, the absence of cancer in breast tissue was likely to be associated with long-term clinical benefits.

On the other hand, the Scottish Medicines Committee was unable to recommend pertuzumab neoadjuvant treatment because of uncertainty in the association between pCR and long-term patient outcomes.

Drug-radiotherapy combinations: what can we learn from progress made from NCRI CTRad Joint Academia Pharma Working Group?

As discussed by Professor Ricky Sharma, Chair of Radiation Oncology at University College London, combining drugs and radiotherapy poses a range of challenges, including choice of endpoints. In 2009, the National Cancer Research Institute (NCRI) established a Clinical and

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[9] FDA (2014). *Guidance for industry. Pathological complete response in neoadjuvant treatment of high-risk early-stage breast cancer: use as an endpoint to support accelerated approval.* www.fda.gov/downloads/drugs/guidances/ucm305501.pdf

[10] EMA (2014). *EMA/CHMP/151853/2014. The role of pathological complete response as an endpoint in neoadjuvant breast cancer studies.* www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/04/WC500165781.pdf

[11] Cortazar P, *et al*. (2014). *Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis.* Lancet. **384(9938)**, 164–172.

Translational Radiotherapy (CTRad) Working Group, which has had a significant impact on the numbers of trials involving radiotherapy, doubling recruitment by 2012/13.

Unfortunately, several large trials of drug–radiotherapy combinations have delivered disappointing results, emphasising the need to consider issues such as the possible use of drugs in radiotherapy at early stages of drug development as well as innovative trial designs. One ray of hope is the apparent success of temozolomide in improving the impact of radiotherapy in a subset of glioblastoma patients.[12] Responses may be enhanced by silencing of the MGMT gene, suggesting a companion diagnostic could be used to identify patients suitable for combination therapy.

Cross-sectoral dialogue

One important goal of CTRad has been to catalyse interactions between key stakeholder communities – industry, academics, regulators and patients – to provide greater clarity on the pathway to approval for new treatment combinations. Workshops were held in 2014 and 2015 to develop and discuss guidance on issues such as trial design and appropriate endpoints. The summary of this work was published as a consensus statement in *Nature Reviews Clinical Oncology*.[13]

The importance of endpoint selection

Appropriate endpoints were an important aspect of these discussions. For radiotherapy, endpoints related to local clearance of disease and the sparing of normal organs from damage are central to treatment success. Hence there are important questions around measuring local control of disease and organ sparing, and how to ensure measures are meaningful to the patient experience. The consensus statement, therefore, included a range of recommendations to guide the choice of primary and secondary endpoints for clinical trials of new drug–radiotherapy combinations.

Professor Sharma also emphasised the importance of defining current standards of care and, where possible, identifying how these were likely to change during the long timescales required to complete phase III randomised clinical trials, and of maintaining a 'line of sight' of the likely pathway to clinical implementation in the future. The consensus statement strongly recommended points of contact with regulatory authorities along the development and clinical evaluation pathway.

The FDA also recommends regular and early contact during development.[14] Cross-sectoral dialogue is continuing, for example through a multidisciplinary FDA workshop due to be held in February 2018 to discuss perceived regulatory barriers and develop further guidance. The EMA is also organising a workshop on local endpoints.

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[12] Stupp R, *et al*. (2009). *Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial.* Lancet Oncol. **10(5)**, 459–466.
[13] Sharma RA, *et al*. (2016). *Clinical development of new drug-radiotherapy combinations.* Nat Rev Clin Oncol. **13(10)**, 627–642.
[14] Walker AJ, *et al.* (2017). *Clinical development of cancer drugs in combination with external beam radiation therapy: US Food and Drug Administration perspective.* Int J Radiat Oncol Biol Phys. **98(1)**, 5–7.

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