PIONEER

innovative medicines initiative

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Prostate Cancer DIagnOsis and TreatmeNt Enhancement through the Power of Big Data in EuROpe

WP6 – HTA regulator – payer integration

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Contents

Publishable Summary

PIONEER Work Package 6 (WP6) has committed to developing a prostate-cancer-specific framework for evidence requirements to support the efficient and targeted use of current treatment options in addition to the appropriate introduction and adoption of new technologies.

Moreover, WP6 will seek to develop reference models for use in economic evaluations and, as a key objective, will explore whether it can develop a core set of reference models for different stages of prostate cancer, or an overarching modelling framework.

Developing alignment, and ideally consensus, amongst regulatory and HTA agencies and payers is an important feature of the work.

The work of WP6 is complemented by Work Package 2 of PIONEER, which is developing standardised definitions of prostate cancer outcomes among different stakeholders in different stages of PCa care; Work Package 3, which is working to enable harmonisation, integration and linkage of multiple big data sets from a variety of sources, using an informatics platform developed by Work Package 4; and by Work Package 5 which will provide a unique toolkit of standard and cutting-edge analytical methods for the analysis of big data sources.

Prostate cancer can benefit from earlier diagnosis and eventually from risk-adapted population-based screening. As more interventions become available, healthcare systems need to ensure they have appropriate frameworks in place to guide decision-making in diagnosis and management at each stage of the disease. The ability to integrate RWE from multiple sources may enhance decision-making, especially as medicines become more personalised.

Therefore, there is a need for frameworks to enable fair and robust assessment and encourage the development and use of innovative technologies. These frameworks should support management of prostate cancer on a pan-EU level.

PIONEER will put a focus on building an evidence framework for regulatory and HTA decision-making. EU-level action has relevance; in particular it would drive alignment of HTA bodies on methodology and evidence requirements, and it could also help alleviate the workload to assess the value of available therapies as the rich pipeline of new therapies/combinations reaches the market and to reassess their value as new evidence becomes available.

This policy paper attempts to identify the issues and find a way through the maze.

Goal of the deliverable

This policy paper attempts to identify the key issues and make recommendations for next steps that will support action and alignment for our prostate cancer evidence framework. During discussions with leading clinicians in prostate cancer and with HTA body representatives, we clarified four key topics that the future evidence framework and reference models should seek to address:

- *Prostate cancer technologies used in early-line settings*: so far, innovative treatments in prostate cancer have only been reimbursed in Europe in metastatic disease settings; new treatments in non-metastatic settings are set to increase in number. In the latter, regulators have approved based on metastatic-free survival as the primary endpoint in clinical trials; however, these medicines have a lower probability (due to setting and duration of underlying disease) of showing benefit in the outcome traditionally favoured by HTA bodies (overall survival).

- *Utilising emerging prognostic/predictive endpoints and tools*: where choices exist, evidence is generally lacking to inform decisions on which treatment to use, at which time and for which patient. Tools related to precision medicine are emerging to guide clinical decision-making in prostate cancer and innovative treatments are likely to need to demonstrate value in targeted patient populations.

- *Adoption of technologies that are accompanied by co-diagnostics*: there are several medicines in development in metastatic prostate cancer that are likely to require the use of a co-diagnostic test to identify patients most like to respond to treatment. By improving targeting of patients, value is likely to be added over current standards of care. However, there are complexities around standardisation and quality control of co-diagnostic testing.

- *Agreeing "value-flexibility" for new technologies when the first (later-line) indication may have the greatest uncertainty but also the highest unmet need*: new prostate cancer treatments are typically initially introduced in last-line metastatic disease where there is the highest perceived unmet need. Regulatory pathways open the opportunity to launch 'breakthrough' cancer medicines based on single-arm Phase II data in populations with a lack of effective options. There is a divergence in the perspective of value between regulators and HTA bodies: regulators focus on relative risk/benefit in each individual indication and patient population, whereas HTA bodies' starting point is the value established in relation to the opportunity cost for the health system. Often HTA bodies struggle to approve the first indications for a given oncology treatment on account of the perceived small gains in outcomes at late-stage disease. Comparatively end stage indications appear to offer low relative value with high uncertainty compared to therapies in other disease areas or in earlier stages of disease. This can lead to difficult decisions for companies: launch where there is high unmet need but little probability of success in HTA?

It is envisaged that an evidence framework, embracing real-world data (RWD) will play an important role in bridging the potentially widening gap between HTAs and regulators across each of these four themes.

While it is true that healthcare remains a Member State competence, the EU as a whole is becoming more involved in various aspects (legislation on in-vitro diagnostics, clinical trials, cross-border healthcare, data protection, HTA and more) which, theoretically at least, span all EU countries.

But the EU cannot act alone. Member States and stakeholders themselves have to adapt, take a look at their procedures and collaborate much more with their fellows across borders in many spheres, including the sharing of knowledge and research (to avoid duplication), and the pooling of RWD.

It is evident that the EU, in tandem with Member States, needs to ensure the proper transposition of its legislation and policies into regulation at national level to reduce the ever-widening gap between regulatory and HTA decisions on innovative medicines. For the delivery of the next milestone on this project, we will

propose roles for RWD and suggest potential proactive solutions that may attempt to bridge this gap.

Big moves are underway to future proof the way EU countries assess new health technology, and this is a fix that, in theory, could bring innovative care faster to patients and protect health budgets by eliminating waste.

When looking at the EU as a whole, the present systems lack consistency and are beginning to creak under the weight of new innovation. Inequalities across Member States in the speed and ability of patients to access valuable innovations need to be rectified.

The aim of PIONEER is to carve a path for innovation by building an EU-wide framework for the value assessment of technologies in prostate cancer, using RWE and utilising stakeholders and policymakers - at regional, national and EU levels.

Policy paper

Executive Summary

PIONEER's goal is to develop, and validate, an EU-wide evidence framework for the value assessment of innovative technologies in prostate cancer, using real-world evidence (RWE). Stakeholders and policymakers will be key to development, validation and onward dissemination of the framework.

Regulators are increasingly recognising the value of RWE when evaluating approval of innovative medicines, as illustrated by new regulatory pathways designed to speed up the (conditional) approval based on relatively limited or immature initial clinical trial data. Health Technology Appraisal (HTA) bodies and payer groups also recognise the potential of RWE, but alignment on how to collect, analyse, interpret and use in healthcare decision-making is lacking.

HTA is key to realising timely patient access to effective medicines and often considers this access in the context of the alternative health gains that might be foregone within a nation's limited health budget as a consequence of recommending a new technology. EU and Member State policymakers canvas a wide range of opinions in support of individual technology appraisals, usually seeking input from clinicians, pharmaceutical companies, payers and patients. Such stakeholders also have valuable insights beyond the individual technology appraisal and can provide important contributions to the process and methods of assessment and appraisal in a particular therapeutic area. This project will work with such stakeholder organisations as well as regulators to establish minimum evidence requirements needed for the assessment of new prostate cancer technologies and will identify, at an early stage, potential uncertainties requiring extra data.

PIONEER will also seek to develop reference models for use in economic evaluations and, as a key objective, will explore whether it can develop a core set of reference models for different stages of prostate cancer, or an overarching modelling framework. It will explore approaches to high-quality RWE collection.

PIONEER will harness the power of big data to transform the field of prostate cancer research from the perspective of all relevant stakeholders including clinicians, pharmaceutical companies, payers and most

importantly patients.

This policy paper attempts to identify the key issues and make recommendations for next steps that will support action and alignment for our prostate cancer evidence framework. During discussions with leading clinicians in prostate cancer and with HTA body representatives, we clarified four key topics that the future evidence framework and reference models should seek to address:

- *Prostate cancer technologies used in early-line settings*: so far innovative treatments in prostate cancer have only been reimbursed in Europe in metastatic disease settings; new treatments in non-metastatic settings are set to increase in number. In the latter, regulators have approved based on metastatic-free survival as the primary endpoint in clinical trials; however, these medicines have a lower probability (due to setting and duration of underlying disease) of showing benefit in the outcome traditionally favoured by HTA bodies (overall survival).

- *Utilising emerging prognostic/predictive endpoints and tools*: where choices exist, evidence is generally lacking to inform decisions on which treatment to use, at which time and for which patient. Tools related to precision medicine are emerging to guide clinical decision-making in prostate cancer and innovative treatments are likely to need to demonstrate value in targeted patient populations.

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It is envisaged that an evidence framework, embracing real-world data (RWD) will play an important role in bridging the potentially widening gap between HTAs and regulators across each of these four themes.

While it is true that healthcare remains a Member State competence, the EU as a whole is becoming more involved in various aspects (legislation on in-vitro diagnostics, clinical trials, cross-border healthcare, data protection, HTA and more) which, theoretically at least, span all EU countries.

But the EU cannot act alone. Member States and stakeholders themselves have to adapt, take a look at their procedures and collaborate much more with their fellows across borders in many spheres, including the sharing of knowledge and research (to avoid duplication), and the pooling of RWD.

It is evident that the EU, in tandem with Member States, needs to ensure the proper transposition of its legislation and policies into regulation at national level to reduce the ever-widening gap between regulatory and HTA decisions on innovative medicines. For the delivery of the next milestone on this project we will propose roles for RWD and suggest potential proactive solutions that may attempt to bridge this gap.

Big moves are underway to future proof the way EU countries assess new health technology, and this is a fix that, in theory, could bring innovative care faster to patients and protect health budgets by eliminating waste.

When looking at the EU as a whole, the present systems lack consistency and are beginning to creak under the weight of new innovation. Inequalities across Member States in the speed and ability of patients to access valuable innovations need to be rectified.

The aim of PIONEER is to carve a path for new innovation by building an EU-wide framework for the value assessment of technologies in prostate cancer, using RWE and utilising stakeholders and policymakers - at regional, national and EU levels.

Introduction to PIONEER and Work Package 6

PIONEER seeks to develop, and also validate, a framework for the value assessment of innovative technologies in prostate cancer using RWE.

As real world health data is being used more and more in real time to help all healthcare actors, in particular healthcare professionals, make better well-informed decisions, it offers a potential source to address evidence uncertainty when granting faster access to innovative treatments, improving outcomes and value for money.

RWD has been defined as “an umbrella term for different types of healthcare data that are not collected in conventional randomised controlled trials... including patient reported data, data from clinicians, hospital data, data from payers and social data”[1]. Its evaluation in the context of rigorous scientific enquiry allows such data to provide RWE of treatment effectiveness.

Regulators are increasingly recognising the value of RWE when making decisions on the safety and effectiveness of new medicines. New regulatory pathways open the door to launching ‘breakthrough’ medicines based on relatively immature clinical trial data, provisional on collection of RWD and its appropriate analysis. The patient perspective is essential to enable complete understanding in these instances. Such processes can allow for multi-disciplinary treatment strategies, so providing each patient the possibility to make an informed choice based on their individual risk-benefit assessment.

HTA bodies and payer groups recognise the potential of RWD, but alignment on how to collect, analyse,

[1] Get Real Glossary https://www.imi-getreal.eu/Portals/1/Documents/01%20deliverables/D1.3%20-%20Revised%20GetReal%20glossary%20-%20FINAL%20updated%20version_25Oct16_webversion.pdf. (Last accessed on May 25th 2019)

interpret and use the output in healthcare decision-making is still necessary. In the context of the specificities of prostate cancer, PIONEER will work with such bodies, as well as regulators, to establish minimum evidence requirements while identifying, at an early stage, potential uncertainties requiring extra data.

PIONEER will aim to ensure that policy keeps up with emerging and fast-moving science.

One question that urgently needs to be addressed in healthcare generally is how evidence can be assessed at an earlier stage to allow common decision frameworks to be set up.

PIONEER Work Package 6 (WP6) has committed to developing a prostate-cancer-specific framework for evidence requirements to support the efficient and targeted use of current treatment options in addition to the appropriate introduction and adoption of new technologies.

Moreover, WP6 will seek to develop reference models for use in economic evaluations and, as a key objective, will explore whether it can develop a core set of reference models for different stages of prostate cancer, or an overarching modelling framework.

Developing alignment, and ideally consensus, amongst regulatory and HTA agencies and payers is an important feature of the work.

The work of WP6 is complemented by Work Package 2 of PIONEER, which is developing standardised definitions of prostate cancer outcomes among different stakeholders in different stages of PCa care; Work Package 3, which is working to enable harmonisation, integration and linkage of multiple big data sets from a variety of sources, using an informatics platform developed by Work Package 4; and by Work Package 5 which will provide a unique toolkit of standard and cutting-edge analytical methods for the analysis of big data sources.

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Therefore, there is a need for frameworks to enable fair and robust assessment and encourage the development and use of innovative technologies. These frameworks should support management of prostate cancer on a pan-EU level.

PIONEER will put a focus on building an evidence framework for regulatory and HTA decision-making. EU-level action has relevance; in particular it would drive alignment of HTA bodies on methodology and evidence requirements, and it could also help alleviate the workload to assess the value of available therapies as the rich pipeline of new therapies/combinations reaches the market and to reassess their value as new evidence becomes available.

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The Burden of Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer in men, with more than 417,000 new cases and 92,000 deaths in Europe every year[2]. Many will develop detectable prostate cancer before the age of 85. More than two million men in Europe are living with this disease. Although diet and environmental factors certainly play an important role, the three well-established risk factors for prostate cancer are increasing age, ethnic origin and family history. In the latter, men with a family history of the disease are at higher risk of developing the condition, yet family history is an often lacking or an insufficiently explored risk factor.

The fact that early stages of prostate cancer are asymptomatic means that there are no clear symptoms to indicate its presence.

Meanwhile, unacceptable inequalities persist in prostate cancer survival, which varies from 88% in Central European countries to 72% in Eastern European countries. Compared with other cancers, these survival rates are high. A characteristic of prostate cancer is that it is regarded as "indolent" in early stages and can be cured. However, once relapse/progression occurs, mortality rates increase dramatically. The variation in mortality between countries may be due to differences in the quality of care or an unequally-applied early detection programme[3].

As noted, the risk of prostate cancer increases with age. Therefore, given the EU's ageing population, the burden on society due to prostate cancer is expected to increase dramatically. In this context, it is perhaps surprising that the research funding available is below other common cancers [4]. This means that progress in the area is slow.

A further issue is that EU Member States have large disparities in prostate cancer incidence and survival rates vary alarmingly from country to country[5].

Given the amount of medical data theoretically available, with prostate cancer it is still the case that there is not enough information on risk factors or patient characteristics, especially regarding those that are at risk of developing metastatic disease. Arguably, the data is out there, as is the genetic information, but it is not being used in the most efficient ways.

As such, the ability to target patients at risk, and which will have the best outcomes via specific treatment regimens, is not yet fully developed. As with many modern-day healthcare breakthroughs, it can be argued that new knowledge is taking too long to be put to effective use on the ground.

Such inefficiency has an obvious effect on optimizing treatment and economics.

[2] Policy Paper on PSA Screening For Prostate Cancer. See following link: http://epad.uroweb.org/wp-content/uploads/EAU_policy-briefing_PSA.pdf (accessed on May 17th 2019)
[3] De Angelis, Roberta, et al. "Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study." The lancet oncology 15.1 (2014): 23-34.
[4] Policy Paper on PSA Screening For Prostate Cancer. See following link: http://epad.uroweb.org/wp-content/uploads/EAU_policy-briefing_PSA.pdf (accessed on May 17th, 2019
[5] Burns, Richeal, et al. "An examination of variations in the uptake of prostate cancer screening within and between the countries of the EU-27." Health Policy 108.2-3 (2012): 268-276.

More on Real World Evidence

Effective evaluation of the medical, social, economic and ethical issues of treatments in a systematic, transparent, unbiased, robust manner will promote safe, effective health policies that are patient-focused and allow healthcare systems to obtain best value - whether at the time of launch or following use in real-life circumstances.

Adapted methods and openness to evidence derived from sources beyond the classical randomised controlled clinical trials will be helpful.

In the case of pragmatic clinical trials, RWD can be useful to detect patient responses to new therapies in real-world settings.

Several national health databases have been providing an opportunity to search, identify, and target anonymised patient data. These data can then go to a healthcare professional to offer him or her integrated real-time updates in the case of national health records.

The practical upshot could be that such databases may allow a radical reduction in the development time usually needed in RCTs.

Cost and Value

Healthcare systems seek to maximise the public health opportunities for the widest populations and will deploy as far as they are able the most appropriate tools – or what they deem the most appropriate tools - to achieve that. For decades, healthcare spending rose steadily in the developed world, in line with the growing prosperity that permitted many countries to continue funding wider coverage of the new diagnostic and treatment regimens that medical science offered. However, economic conditions in the past 10-20 years have meant an increasing focus on value for money, and arguably an increased emphasis on short-term cost impact rather than investment in interventions to secure improved long-term outcomes.

One obvious emerging factor is the ageing of the population. The burden on health and social care spending is greater than ever before because people are living longer – thanks in many cases to the advances in healthcare. Citizens are living longer and suffering more disease, particularly as previously incurable diseases have become chronic, long-term conditions accompanied by multiple morbidities, with consequent strains on resources. The skewed distribution of healthcare demand is well known, with the vast majority of spending concentrated in the final years of life as health declines and as co-morbidities and concurrent interventions proliferate.

Another factor is scientific, technological and medical progress, putting further strain on limited economic resources, matched by an inertia within healthcare systems preventing disinvestment in old, often ineffective treatments and practices that could allow headroom for innovation.

As we close in on the start of the third decade of this century, society and its appointed leaders, faced with numerous new and valuable diagnostic and therapeutic options are recognising that new treatments usually involve increased costs, but are concerned with the level of certainty around the long-term value that balances

benefits to the patient, delay to longer-term health care costs, and the opportunity cost to other areas of healthcare.

Innovators have another view of the world: they are conscious of the potential merits of their innovations and of the efforts expended to achieve them; they will also have a view of what sort of return is required, both to reward the individual innovation, but also to support re-investment into the expensive infrastructure that makes future innovations possible.

Regulators bring another perspective. They are essentially gatekeepers on what is made available to help improve the health of the population. They operate on the basis of standards of quality, safety and efficacy for the goods and services that are proposed as serving the public interest.

Patients also have a key role. They, and their care-givers, will have a clear view about what is valuable to them - a complete cure, longer life, quality of life, the choice (sometimes) between one or the other - even helping others through sharing their personal health data.

Meanwhile, social expectations, social values, the way society feels about balancing individual needs against public needs also come into the 'value' equation, as do rewarding innovation, priorities in public spending, and so on. These all contribute to the climate in which healthcare systems - and indeed regulators and innovators - make choices and plan strategies.

Health Technology Assessment (HTA)

HTA plays a huge part in these issues. The ultimate goal of HTA is to improve patients' access to effective medicines, whilst considering the alternative health trade-offs that might be forgone within a nation's health budget. This is of concern for national health representatives, Member State healthcare payers, MEPs, medical experts and governing bodies - as well as industry, scientists, researchers, and of course patients. At its best, HTA presents information about the medical, social, economic and ethical issues related to the use of a new health technology in a systematic, transparent, unbiased and robust manner. It can inform decision-makers on the formulation of safe, effective health policies that achieve best outcomes and value for money for patients, health professionals and health systems. It helps promote sustainability in the healthcare system but also the use of innovative products directly benefiting patients.

Whilst there are some similarities across Member States, HTA is highly individualised for each healthcare system, despite 20 years of partial cooperation among Member States. A current priority of the European Commission to improve collaboration on HTA matters, and the European Commission Relative Effectiveness Working Group, created under the Pharmaceutical Forum, is an example of this[6].

[6] Core principles on relative effectiveness (Pharmaceutical forum - Working Group on Relative Effectiveness). See following link: https://ec.europa.eu/docsroom/documents/7581?locale=en. Accessed on April 17th, 2019

Several countries are still opposed to the Commission proposals with respect to mandatory EU joint action on HTA (despite the European Parliament largely backing it). These include heavyweights France and Germany.

Part of the reason for the Commission's proposals is to reduce unnecessary repetition across the EU, build on the exemplar work of European Network for Health Technology Assessment (EUnetHTA) as well as boost efficiency and reliability of results.

The Austrian Presidency tried extremely hard in the latter part of 2018 but ultimately failed to make a breakthrough. Given that situation, the Romanian presidency has deliberately chosen to deal with the technical aspects only. Finland will take up the reins from 1 July.

The Parliament's vote in Strasbourg in November to back legislation for EU-level HTA was broadly welcomed by many stakeholders, but, despite such positivity, several Member States raised subsidiarity concerns in an area, healthcare, that comes down to closely guarded national competence. A compromise seems a long way off, but, at the very least, the hope is that all will be resolved before Croatia takes over the reins on 1 January, 2020.

By conducting joint clinical assessments, economies of scale, greater business predictability, increased quality and consistency and improved transparency for patients should be achieved in the long run. Despite positivity from the European Economic and Social Committee, and the backing of the European Parliament for the mandatory parts of the European Commission's proposal[7], several Member States objected, some raising subsidiarity concerns in healthcare, reflecting closely guarded national competence. Obviously, this is a big topic, and all stakeholders have been watching events closely, not least now that it has reached Council level.

The PIONEER project will be engaging with the Commission and Parliament in the wake of the May 2019 European elections, as well as following up with Member States.

Given PIONEER's aim of encouraging stakeholder alignment, it is worth noting here that several groups across the EU - notably the Valletta, BeNeLuxAIr, and FINOSE groups - are working together to negotiate lower drugs prices using the power of dealing with pharmaceutical companies together rather than separately.

BeNeLuxAIr (Belgium, Netherlands, Luxembourg, Austria and Ireland)

In 2016, the Belgian, Dutch, Luxembourg and Austrian governments declared their intention to collaborate on pharmaceutical policy, more precisely on horizon scanning, HTA, information sharing and policy exchange, and pricing and reimbursement. It is the goal of the collaboration to avoid duplication of efforts by dividing tasks and sharing data. Later, Ireland joined the collaboration.

The Valletta Group (Italy, Spain, Greece, Portugal, Slovenia, Cyprus, Malta, Croatia and France as an observer)

The Valletta Group was established in May 2017 with the intention to, among others, guarantee patients access to new, innovative treatments and ensure sustainability of the participating national health systems. Apart from exchanging best practice across the countries, the collaboration is engaged in the following

[7] Regulation of the European Parliament and of the Council on health technology assessment and amending Directive 2011/24/EU. See following link: https://ec.europa.eu/health/sites/health/files/technology_assessment/docs/com2018_51final_en.pdf. Accessed on April 25th, 2019

different activities:

- Gathering and sharing information (e.g. policies and reimbursement decisions)
- Horizon scanning of innovative medicines and treatments
- Joint clinical assessments and economic evaluation
- Exploring joint price negotiations

FINOSE (Finland, Norway, Sweden)

FINOSE was launched on March 27th, 2018. The overall intention of the collaboration is to ensure earlier access to medicines through cooperation on assessment of relative efficacy and relevant parts of the health economic framework. A joint team across the three countries will be assigned to share work for accepted applications and reduce the regulatory burden on both the agencies and the applying pharmaceutical companies (i.e. simultaneous submission to the three agencies). The access and reimbursement decision is still subject to the individual agencies' national regulations country-by-country. FINOSE is now receiving applications for joint assessment and the pilot will run until 2020.

Visegrad (Czech, Hungary, Poland, Slovakia, Croatia, Lithuania)

The mandate of Visegrad is still relatively unclear and no participants visited the conference.
However, the collaboration has indicated an intent for joint price negotiation.

Thanks to some degree of European cooperation on HTA down the years, patients suffering from rare diseases have better access to medicines and treatments that are effective for their condition[8]. The opportunity is also there for Member States to access a large pool of clinical trial data.

Health and Food Safety Commissioner, Vytenis Andriukaitis, has said that under current EU plans, national authorities will be able to further pool their resources, and industry will benefit from increased predictability.

In reality, it is not surprising that the proposal for greater coordination of HTA generates some nervousness. The EU is still feeling its way in health policy, so just as with baby steps, there is natural caution over progress. But progress is - as everyone involved admits - necessary.

The Issue

Europe needs affordable and sustainable patient access to new health technologies. EU-level actions with the focus on a common assessment of the relative effectiveness of a technology can add value if they avoid unnecessary duplication as part of HTA in individual Member States and enable greater clarity, lead to an improvement in standards of methodological and process aspects, improve predictability, and contribute to better and timely access of health technologies to patients.

Given substantial differences in how HTA is conducted and used in national decision-making, collaborative, European efforts are best suited at the level of the clinical aspects of HTA. Patients have valuable perspectives and experience that can inform HTA decision-making, helping to explain what it is like to live with a condition, experience with current technologies and what they would most value in a new treatment. The active involvement of patients will result in technology assessments of higher quality that are more widely accepted and stand a greater chance of being implemented

[8] Why EURORDIS supports the proposal for a Regulation on Health Technology Assessment (HTA) Cooperation in Europe. See following link: http://download2.eurordis.org.s3.amazonaws.com/positionpapers/Statement_final.pdf. Accessed: April 17th, 2019

PIONEER has committed to developing a prostate-cancer-specific framework for evidence requirements to support the efficient and targeted use of current treatment options in addition to the appropriate introduction and adoption of new technologies. Developing consensus amongst regulatory and HTA agencies and payers is an important feature of the work. The remainder of this paper focuses on future HTA scenarios that are likely to challenge current HTA process and highlights the need for the development of a core set of reference models that can be used for economic evaluations in prostate cancer. The models developed will likely need to be tailored for different stages of the disease and should utilise best methodologies in economic evaluation and optimise the use of RWD collection.

During discussions with leading clinicians in prostate cancer and with HTA body representatives, we clarified four key topics that the future reference models should seek to address. Our discussions on these topics raised key questions that will help us ensure the models developed are future-proofed and flexible to accommodate new technologies on the horizon where appropriate. The four topics of focus that were agreed should be accommodated in the reference models are:

- Prostate cancer technologies used in early-line settings
- Utilising emerging prognostic/predictive endpoints and tools
- Adoption of technologies that are accompanied by co-diagnostics
- Agreeing “value flexibility” for new technologies, when the first (later-line) indication may have the greatest uncertainty but also the highest unmet need

New technologies in early line settings: So far, novel treatments in prostate cancer have only been reimbursed in Europe in metastatic disease settings, and these approvals have been accompanied by a statistically significant added benefit in overall survival (OS). Recently, two novel treatments have received the first EU regulatory approvals in a non-metastatic prostate cancer indication, with a third treatment likely to follow later this year. As agreed with the regulators, all of these treatments had metastatic-free survival (MFS) as the primary endpoint in their pivotal RCT; none have achieved statistically significant overall survival (OS) benefit. This trend is highly likely to accelerate with more approvals in other non-metastatic indications expected in the next five years and low probability of observing a statistically significant OS benefit – indeed it could be argued that this is irrelevant to proving value in these earlier settings due to the average patient life expectancy. In our discussions, clinicians re-iterated that traditional endpoints, such as OS, are not relevant to treatment of early prostate cancer. To establish validated surrogate endpoints that will be acceptable to national authorities and payers, RWD is needed providing evidence of association; this will require large databases, collaboration across countries and cooperation from industry. This is not a novel approach, as similar surrogate endpoints have been established in other cancers, and we will need to pull on these learnings in prostate cancer. HTA bodies agreed new approaches are needed, but also acknowledged that each case should be taken on its own merits, and uncertainty needs to be accounted for. Risk sharing and collection of RWD were flagged as tools to address uncertainty. All stakeholders consulted agreed that this is a priority topic to consider when constructing the reference models, which may necessitate different models being required for difference disease stages.

Utilsing emerging prognostic/predictive endpoints and tools: As more innovative treatments are approved, the choices available to clinicians increase; however, evidence is generally lacking to inform decisions on which product to use, at which time and for which patient. New tools related to precision medicine will become available to guide clinical decision-making in prostate cancer:

- Next-generation imaging
- Clinical and non-clinical biomarkers
- Genetic profiling and co-diagnostics

It is highly likely that innovative treatments will more frequently demonstrate value in targeted patient sub-populations in order to achieve timely HTA approval/reimbursement. Clinicians shared that prostate cancer is relatively immature in applying precision medicine. Whilst PSA is a good overall measure of response to treatment, biomarkers to predict response to treatment are lacking and much needed. Evidence is scarce and all stakeholders acknowledged this was an important issue that needs further exploration and development. With authorities requiring high standards of evidence, finding predictive biomarkers will take time. One gap between regulatory and HTA decision-making is the level of uncertainty in the evidence, and for HTA bodies, certainty around value and expenditure is uniquely important. For regulators, evidence gaps can be filled by post-marketing studies, whereas HTA bodies want more decision certainty at time of assessment. Monitoring genetics/phenotypes may help speed patients to the right treatment, and we will need to explore how RWD sources can support this objective. A further consideration is that, for a growing proportion of new technologies, there is a need to re-focus away from traditional sub-groups within a cancer type, and towards patients with a specific disease marker who can be treated using a targeted approach, regardless of the tumour type. Redefining the disease by the underlying mechanisms causing the cancer will involve the use of diagnostics and could include biomarkers that define the patient type. This generates parallels with rare or ultra-rare diseases, where traditional RCT evidence may not be desirable or possible and where managed entry agreements and RWD collection are used to manage risk.

Adoption of technologies that are accompanied by co-diagnostics: There are several medicines in development in metastatic prostate cancer that are likely to require the use of a co-diagnostic test to identify patients most likely to respond to treatment. By introducing a co-diagnostic, only a targeted number of patients will use the medicine, and the response is anticipated to be of added value compared to standard of care in these patient sub-populations. Co-diagnostics introduce additional costs and process steps into the care pathway. The infrastructure to support co-diagnostics use is in development with many countries taking a bespoke approach. Guidelines will need to be developed to recommend when and how often testing should be performed.

Clinicians agree that use of co-diagnostics (CDx) as part of routine management would be of great benefit. However, there are complexities around the standardisation and quality control of CDx testing. Patients should have access to testing; however, quality needs to be assured in the range of tests that may be available to minimise variability. To establish these standards and achieve professional consensus, RWD could be generated in thousands of patients, necessitating cross-country collaboration with appropriate legal and financial support. Harmonisation across CDx suppliers may also be challenging and could take time. Ideally validation of testing would be developed from a single biomaterial data source such as a European repository, but this may be challenging, not just technically but politically. Similarly, HTA bodies agreed the topic is relevant and timely. The view was expressed that CDx is not part of treatment but should identify the need for treatment; and there should be clear separation between treatment and diagnostic, including separate funding routes. EU standards for quality and specificity are needed, and solutions may include finding suitable centralised provider(s).

Panel testing, whereby one test is undertaken for a broad range of potential markers, may be more efficient than testing for each biomarker and more suited to targeted and combination treatments. This is being considered by the health service in England in a drive to include genetic testing as part of routine care. Over time, mechanisms would need to be found to add new markers and provide funding. The cost of adding new markers to the panel vs. adding a new test would be a consideration. As treatments move earlier in disease pathway, testing recommendations will also need to evolve.

Agreeing "value flexibility" for new technologies: Regulatory pathways open the opportunity to launch 'breakthrough' cancer medicines based on single-arm Phase II data in populations with a lack of effective options. Expansion of clinical development plans from these Phase II studies (with registrational potential) in selected populations provides a potential route to early patient access, clinical experience and an opportunity for further disease understanding. Regulatory bodies welcome these new treatments as long as the benefit and unmet need for the population are clear.

The divergence in value comes from the differing approaches of regulators versus the HTA bodies. Regulators focus on relative risk/benefit in each individual indication, whereas HTA bodies' starting point is the value established during the appraisal of the first indication bought to market. New prostate cancer treatments are typically initially introduced in last-line metastatic disease where there is the highest perceived unmet need, and hence the value of the technology is established in the last-line indication and dictates the starting point for value discussions of earlier-line indications. Often payer appraisal of late-line treatments is that they offer low relative value with small incremental benefit, and with higher uncertainty due to non-RCT data. Understandably, payers are focused on certainty and expenditure around introducing medicines in last-line settings; and, acknowledging that treatment of patients in this setting is an emotional issue, clinicians often feel the need to do something. This may be expensive where outcomes remain uncertain and unsatisfactory for clinicians and their patients, especially when there are few, if any, alternatives.

Manufacturers therefore face a dilemma when bringing new products to patients in these last-line indications. The regulators may approve based on benefit and high unmet need, but there will likely be a low probability of success with HTA, which will have potential long-term knock-on implications for other earlier-line indications in prostate or other tumour types. Whilst the value to patients in last-line indications is clear (they have no further options), manufacturers are cautious about launching with Phase II data given the low probability of success with HTA/payers. Both HTA and clinical stakeholders agreed there are key differences/contradictions in the regulatory and HTA pathways. Clinicians suggested that using RWD following introduction of a medicine in these last-line indications may help to fill evidence gaps and provide valuable information on patient targeting and treatment algorithms. In these last-line indications it will also be important to capture patient outcomes, and the patient perspective on the value the new technology offers over and above standard treatments. All stakeholders agreed on the need to put patient safety first and to only approve treatments with a clear benefit to patients. The use of targeted RWD collection, conditional approvals and EU-wide managed access agreements were suggestions worth considering as we build the reference models for last-line treatment settings.

Evidence, Evidence, Evidence…

As said above, evidence requirements are different for regulatory versus HTA bodies. Regulators evaluate the quality, safety and efficacy of new medicines and balance the risk vs. benefit of an individual product in a particular patient population. HTA bodies assess evidence of benefit vs. the costs associated with that benefit in order to make a judgement on value for money, affordability and opportunity cost in the context of the wider health system. The challenges of finding appropriate endpoints, which may vary according to the disease stage in prostate cancer and line of treatment, as well as delaying patient access while waiting for the results of long-term studies, have been acknowledged by both regulators and HTA bodies.

For regulators, when there is satisfaction of the basic benefit/risk profile, evidence gaps (often related to safety) can be filled by post-marketing studies but HTA bodies want more decision certainty at time of assessment. Some HTA bodies are embedding a data-driven approach where evidence at launch is sub-optimal for a definitive decision. In these cases, when any uncertainty can be addressed with new data, a managed entry agreement will allow patients access to the medicine following an initial appraisal, on the condition that the preliminary decision is revisited within an agreed timeframe, utilising new evidence generated in both the real world and from ongoing clinical trials. This may be of particular use for treatments launching in last-line indications or for those targeting small sub-populations which will have limited evidence at launch.

The use of large, robust patient registries in prostate cancer would support the decision-making process, inform clinical practice, and could provide information about long-term adverse events. Given the associated costs of patient registries, it is crucial to set them up in a flexible way to collect sufficient data and to account for the evolution in patient populations and treatment strategies.

At present, many registries are collecting data only on a specific technology or service because their manufacturers are the only source of funding. More sustainable disease- rather than technology-focused registries will only be established if the current lack of public funding for data collection initiatives can be overcome.

There is a great and urgent need to break the current country-specific gridlock around data protection and develop a transparent regulatory and governance framework that supports the need to improve personal and global health while respecting individuals' right to control their personal data.

Again, legislation needs to catch up with science.

Evaluation of clinical effectiveness and analyses of long-term treatment effects depend on availability of quality assured clinical registries for observational studies. No single entity has the depth of knowledge and financial resources to effectively collect and mine the biomedical data needed to enable personalised medicine. New forms of collaboration are required between academic centres, the pharmaceutical industry, regulators and payers.

Of course, data must be of sufficient quality, characterised, standardised, and compatible to allow integration from multiple sources. Storage could also become a limiting factor without adequate action, as could re-use of personal data without adequate arrangements for consent of data originators, along with a range of other data-sharing considerations - including overcoming commercial barriers. And, crucially, professionals must be trained to develop and implement technology solutions.

Conclusions

PIONEER has committed to building an evidence framework to drive towards alignment of regulatory and HTA decision-making.

We have outlined four key evidence themes, related specifically to prostate cancer, which – if left unchecked - we predict will lead to a widening of the gap between regulatory and HTA decisions on innovative medicines.

This project will use the four themes to provoke the debate on the role of RWD and potential proactive solutions that may attempt to bridge this gap. Big moves are underway to future proof the way EU countries assess new health technology, and this is a fix that, in theory, could bring innovative care faster to patients, and protect health budgets by eliminating waste.

When evaluating the EU as a whole, the present systems lack consistency and are beginning to creak under the weight of new innovation. Inequalities across Member States in the speed and ability of patients to access valuable innovations need to be rectified.

Solving these problems is a must.

In the case of prostate cancer, PIONEER's core focus (diagnosis, early treatment and hopefully where appropriate management) needs to make the most of new technologies and develop a new system with which to do this. The aim of PIONEER is to carve a path for new innovation, by building an EU-wide framework for the value assessment of technologies in prostate cancer, using RWE and utilising stakeholders and policymakers - at regional, national and EU levels.

We often say that policy needs to keep up with science, but sometimes it is also true that stakeholders need to keep up with policy and make the best use of it. This is better done together.

Stakeholders must remember three key words: Align. Align. Align.

Repository for primary data[9]

Publication will be via Pioneer website and partners website

[9] Suggested headings

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