Summary of Discussion

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Current and Future Challenges of Innovative Oncology Drugs Development

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SESSION 1 – POSSIBLE AVENUES TO SPEED UP PATIENT ACCESS

EUnetHTA as a possible avenue to speed up patient access

Anne Willemsen (EUnetHTA, NL)

The Cross Border Directive (2011) is the political and legislative framework for the European Network for Health Technology Assessment (EUnetHTA). EUnetHTA was established to facilitate an efficient European HTA landscape through collaboration. Key products follow the life cycle of technologies: Early Dialogues, Joint Relative Effectiveness Assessments (REA), Post Launch Evidence Generation.

In the current Joint Action 3, EUnetHTA has produced 18 pharmaceutical Joint REA on a variety of therapeutic areas, of which 7 considered oncology compounds. EUnetHTA demonstrated that the production process is predictable and of high quality.

Of the EUnetHTA partners that produce or contribute to HTA, many indicated that EUnetHTA REAs were used on a national level. However, the extend of usage varied greatly. Some agencies reported reduced national assessment timelines, others only used the EUnetHTA REA as background information. To enhance impact of these REAs on the timeliness of national assessments, EUnetHTA places more focus on the applicability of the scope of the pharmaceutical REAs. This happens by means of topic prioritisation, a defined specific research question or PICO (Population, Intervention, Comparator(s), Outcomes) related consultation process, and a link with Post Launch Evidence Generation.

Although European collaboration in the field of HTA on pharmaceuticals can be a key instrument to speed up patient access and to pool expertise and knowledge, several steps need to be taken to enhance this process. How can EUnetHTA's pharmaceutical Joint Assessment impact the speed to patient access at a national level?

The role of patients in drug development and innovation - from patient involvement to patient partnership

Sabrina Hanna (the cancer collaborative, CA)

Patient centricity is one of the most pressing priorities for healthcare and life sciences organizations. However, most fall short of being truly patient centric. One of the most critical factors across the lifecycle of a drug is the patient experience. Despite this knowledge, patients are not routinely invited to be partners throughout the continuum. An indiscriminate use of terms is interchanged, rendering them too vague to be meaningful or effective - including patient involvement, patient engagement and patient partnerships.

Patient involvement relates to the consultation with patients, without impact on their outcomes.

Patient engagement is the act of involving patients and caregivers in decision making, design, planning, delivery, and evaluation of health services, when patients are actively engaged.

Patient partnerships are partnerships in medicines research and development, regulatory review, and market access decisions. So, working with patients towards the same/shared objectives. Patients become part of setting the agenda.

Patient centricity, is the recognition of the needs of an individual patient or distinct patient population and their specific needs in the focal point in the overall design of medicine, including the targeted patients' physiological, physical, psychological, and social characteristics.

To fully realize patient centricity, and the potential it offers in biopharmaceutical innovation and faster approval, organizations must be able to truthfully define how they interface with patients, patient advocates and expert patient advocates.

Speeding up access to innovative cancer drugs. Why and how?

Bert Boer (Erasmus University Rotterdam, NL)

Why is speeding up important? What is the tension behind the question? All is driven by the notion that as long as easy cure is not achievable, there will be a need for improvement. What are the mechanism and motives of individual people, and of organisations? How do they perceive the current hurdles? It is important to ask the right questions, based on the right, fair, timely and applicable criteria. In the end the assessment of new cancer drugs, devices, and technology, is based on values. These relate to a benefit/risk ratio. Apart from these content related values, the values of procedures and systems also play a role, the latter should be evidence based, consistent, transparent, and reproducible. And finally, costs will have to be considered. Regulatory authorities and industries partly have overlapping interests and values. Industry on top of these must serve its shareholders. This concept can be extrapolated to other stakeholders in healthcare as well. But focus may be different among the various stakeholders, leading to heterogeneity of values.

How can we deal with these? Central in this discussion is the question of Necessity. At the Erasmus School of Health Policy and Management, an empirical study of coverage policy in the Western World was performed, that identified a large number of sub-questions on the main question of Necessity. For full details please read the thesis "Weaving Necessity" of dr. Kleinhout, at http://hdl.handle.net/1765/129372.Essential elements in the process of appraisal include:

- The acknowledgement of the right, the legitimacy, and validity of all arguments brought forward.
- The acknowledgement of the explicit interplay of all multidimensional, heterogeneous arguments.
- Formulation and try-out several policy options and several lines of argumentations, and to do so explicitly.

Applying these elements to the assessment and access policy, in an open discussion, accepting the difference in priority of important interests of different stakeholders, seems key. Consider all stakeholders as partners, rather than opponents. Find the area of overlap, in the respective interests.

Industry perspective

Ansgar Hebborn (Roche, CH)

There is a major difference between countries in the EU in the availability for patients of newly approved drugs with a focus of concern on Eastern-Europe. For oncology drugs, the situation is better, but still geographically imbalanced. The delay between market authorization and patient access for oncology drugs varies from 2,5 months – over 2,5 years.

A second challenge is the changing face of biomedical innovation, with a.o. an increasing fragmentation of diseases into rare entities, a corresponding necessity in trial design adaptation, the use of surrogate endpoints, and the need for biomarker co-development.

In addition, there is a range of interrelated factors, that contribute to access delays with differences among EU member states:

Category	Potential root causes
The time prior to market authorisation	1. The speed of the regulatory process 2. Accessibility of medicines prior to marketing authorisation
The price and reimbursement process	3. Initiation of the process 4. The speed of the national timelines and adherence
The value assessment process	5. Misalignment on evidence requirement 6. Misalignment on value and price 7. The value assigned to product differentiation and choice
Health system readiness	8. Insufficient budget to implement decisions 9. Diagnosis, supporting infrastructure and relevance to patients
Delay from national to regional approval	10. Multiple layers of decision-making processes

Another major reason for the inequality in access relate to economic readiness of healthcare systems. There is obvious room for improvement, and together we can do better. Europe's Beating Cancer Plan will certainly be of help.

Fast and broad patient access is achievable, and for instance achieved in Germany. This could serve as example. In the HTA process and decision making, it is important to have appropriate understanding of patient expectations and preferences. Also, Health-Related Quality of Life Research (HRQoL) will help to improve patients perceptions of care.

Another element is the provision of care, were healthcare professionals also use their own clinical guidelines. A question is, if HTA and decision-making processes can be more systematically engaged, and whether instruments like the ESMO Magnitude of Clinical Benefit Scale (MCBS) could close the gap? Currently, there are still considerable differences between countries in the acceptance of clinical evidence by decision makers. A European collaboration and HTA legislation, could help advance the issue of access. Importantly, it remains key to prevent that poor legislative compromises add new layer of complexity to current patient access pathways. Post-marketing registries will provide additional and important data.

Pricing and parallel trade issues will also have to be dealt with, in the aim for equal access.

The recent EU plans and strategies do provide opportunities we should take advantage of. But we will need a dedicated **Forum on unequal access**, to talk about the root-causes of inequality in patient access, and to help find solutions.

Breakout group discussions

Breakout Group 1:

- Focused on HTA.
- In view of the currently perceived fragmentation (countries, organisations, stakeholders), to smoothen the process, and speed up further, there is a need for:
    - International collaboration and dialogue
    - Further strengthening active involvement of patient organisations (rather than individual patients) in the HTA process
    - Identification of best practices, that could help in harmonizing the process, wherever we can.

Breakout Group 2:

- What is the status of mandatory reporting of clinical trials and their results?
    - Questions of completeness of reporting
    - Industry research vs academic research
    - EU vs US databases
- How can involving Patient Advocacy Group (PAG's) improve patient access?
    - Show-case of PAG involvement in NICE-assessment of Imatinib in CML.
    - Early involvement of PAG's in PICO definition
- Can lessons be learned from the approval of COVID-vaccines?
    - Different regulatory pathways taken.
    - Different requirements and trade-offs.
    - Rolling-review options.
    - Could some harmonization be possible?

Breakout Group 3:

- Cost and price remain most important issues.
- Acknowledge that industry has responsibilities towards shareholders.
- Clinical data that can inform on reimbursement/pricing, are often missing at the time of initial marketing authorization.
- Data on treatment optimization are relevant for patients and health professionals, healthcare systems, industry and more.
- The UK Cancer Drug Fund can serve as an example of a way to require further clinical data to be generated.

SESSION 2 – CDDF WORKSHOPS IN 2021

Why do we have endpoints in clinical trials?

Axel Glasmacher (Univ. of Bonn; CDDF Board, DE)

This presentation introduced the virtual CDDF Multi-Stakeholder Workshop, April 26-28, 2021. As an appetizer to the topic the CDDF presented a webinar on **matching endpoints to objectives in clinical trials**. which explored the 'replication crisis', the huge failure rate of clinical trials moving from the exploratory to the confirmatory setting. The ICH E9 R1 Consensus Guidelines has put forward the so called Estimands framework. Estimands are defined as a precise description of the treatment effect, reflecting the clinical question posed by the trial objective.

Should overall survival always be the primary endpoint? PFS or similar endpoints have been used as primary endpoint for the approval of many innovative drugs. While on one side alternative endpoints like PFS avoid long study durations, enable a clearer assessment of the treatment effect and are independent of the subsequent therapy, counter arguments should be considered: Overall Survival remains as the most important outcome for patients, and alternatives are not necessarily correlated with overall survival or clinical benefit.

Both the FDA and the EMA have developed **expedited approval pathways** which are mostly used for last line cancer patients with no approved therapeutic alternative and have used endpoints that were 'reasonably likely to predict clinical benefit'. Durable responses fulfil these criteria, albeit rarely in isolation. These early results must then be confirmed in a randomized trial with appropriate time-to-event endpoints. HTA agencies have reported on the difficulty to assess the clinical and economic evidence in the absence of randomized trials.

While all stakeholders seem to agree on the importance of measuring **patient reported outcomes** (PRO's), many would say that their collection is burdensome, and their reliability questioned. The workshop will explore innovative strategies to improve the use of PROs.

Q&A and Discussion

- Given differences in mechanism of action of drugs and in disease dynamic, endpoints of clinical trials will remain a dynamic entity. Intermittent endpoints that can be proven to truly reflect overall survival, are accepted as endpoints used for marketing approval in various diseases now. So, developing such endpoints should be a focus. Keeping focus only on overall survival, would bring drug development to an end.
- Subsequent therapies will influence overall survival, which is another reason to stress the above bullet point. Estimands can be supportive element in this. Maybe even for the assessment of QoL endpoints and PRO's.
- Whether Real World Data could replace the control arm of a formally randomized trial, remains questionable (also see SESSION 5 – REGULATORY HOT TOPICS).

Digital Tools and AI in oncology drug development

Dónal Landers (Digital Experimental Cancer Medicine Team (DECMT), CRUK Manchester Institute, UK)

The development and adoption of digital tools and AI in oncology drug development is challenging from several different perspectives, including cultural issues relating to the acceptance of new technologies, the ethics of utilising AI and digital tools, their integration with current clinical care pathways and whether they really have the potential to deliver real patient benefit.

It is important to recognise that while AI and digital tools present us with an unprecedented opportunity to evolve the delivery of drug development through augmented clinical decision making, it remains crucial to fully understand their limitations and how complex they are to implement.
Intelligence can be defined as the ability to learn and understand, or to deal with new or trying situation. Artificial intelligence is complex to define but can be defined as the science and engineering of making intelligent machines, especially intelligent computer programs. So, these are systems, that can think and act humanly and rationally. The taxonomy of AI a.o. covers machine learning, deep learning, statistics, and logic. And these subsets can be further sub-settled.

There are many challenges in translating AI to the clinic, that still need to be addressed. These include delivery, outcomes, algorithms, training and test data, and implementation of AI in an experimental cancer medicine setting using real examples. One of the examples is the CORONET.AI study, which has developed an algorithm, as part of a decision support system, to assist clinicians in identifying whether to admit a COVID-19 cancer patient to hospital for treatment. We also developed a methodology that the digital ECMT has designed and implemented for several technology studies – the 'Technology' clinical trial – a way of formally testing and validating both digital tools, devices, and AI under robust clinical study conditions with clearly articulated hypotheses. The aim is to develop this tool into a clinical care pathway.

Q&A and Discussion:

- Bias in AI is still an option and relates to the selection of data sets.
- It is conceivable to build an algorithm that helps to reduce population heterogeneity in clinical trials, but it would have to be validated and we are still a long way off.
- Regulatory Guidance on algorithm applications still must be developed.

SESSION 3 – CANCER DRUG DEVELOPMENT IN A GLOBAL SETTING

Pharmacogenetics in oncology

Ron Mathijssen (Erasmus MC, NL)

To implement 'personalized medicine' in oncology practice, tumour characteristics, patient characteristics (such as body composition, gender, age, etcetera) both need to be balanced and considered. Evidently, without appropriate exposure, there will not be an effect. From this adequate exposure the best benefit/risk balance will have to be pursued. So, this requires knowledge on how exposures are achieved, for all drugs that we use. This also introduces the principle and relevance of pharmacogenetics, for which 5-FU is used as a showcase.

Pharmacogenetics involves polymorphisms (usually single-nucleotide polymorphisms; or SNPs) in genes coding for enzymes or drug transporters involved in the metabolism of drugs. Within the field of cancer therapy, pharmacogenetics can be used to determine a safe (starting) dose for a specific anti-cancer agent. The example of (*DPYD)*, the gene coding for the enzyme DPD (dihydro-pyrimidine-dehydrogenase) can be taken to stress the importance. In 3-5% or the western population, DPD is not or only partly functional. There are 4 different polymorphisms involved, with different relative risks. However, in all cases DPD deficiency disrupts the benefit-risk ratio and leads to excessive toxicity. Based upon a large prospective Dutch study (Henricks LM et al, Lancet Oncology 2018; 19:1459-1467), this pharmacogenetic phenomenon is now used in the Netherlands, to guide dosing. So, in the above case, the focus is on the avoidance of excessive toxicity. Since the study only involved a western population, a study in an Asian population was recently started (https://clinicaltrials.gov/ct2/show/nct04300361). Similar toxicity related polymorphisms are relevant for TPMT*2/*3 and 6-MP, UGT1A1*28 and irinotecan and CYP3A4*22 and sunitinib/pazopanib.

Pharmacogenetics may also be used to understand why – sometimes – it is impossible to achieve an adequate exposure to a drug. This is exemplified by use of the agent tamoxifen in the adjuvant treatment of breast cancer. Tamoxifen is an inactive pro-drug and needs to be metabolized via CYP2D6 to the active metabolite endoxifen. SNP's related to this enzyme, that are known to involve 20% of the population, will lead to decreased metabolism, and thus decreased and/or below-threshold levels of active drug.

It may therefore be interesting, to guide drug treatment, with the introduction of a "DNA passport" on SNP's.

As mentioned, and unfortunately, most of the genetic studies performed so far are done in (mainly) Caucasian cancer patients. This means that it is largely unknown how other ethnicities will respond to a drug, as genetic polymorphisms may differ largely among ethnic groups.

Tumour Agnostic Drug Development and Tumour Agnostic Re-use of Registered Drugs

Richard L. Schilsky (American Society of Clinical Oncology, USA)

In the current era of precision medicine, tumour agnostic drug development is feasible when a drug exerts similar pharmacologic and clinical effects in a range of tumour types that have in common a drug target that can be reliably identified by an analytically validated biomarker test. Since 2017, 3 drugs have received tumour agnostic approvals in 4 indications by the FDA (pembrolizumab in MSI-H tumours, and in tumours with high mutation burden, larotrectinib and entrectinib each in solid tumours with *NTRK* fusions).

Approvals were generally granted based on results of single arm phase 2 trials that enrolled a variety of tumour types and demonstrated substantial and durable clinical activity (i.e., objective responses) and acceptable safety in patients with advanced disease and unmet medical need. Safety has been shown in a sufficiently large data set but given the fact that small numbers of particular patient populations in the subsets of the various trials preclude a solid assessment of benefit in those subsets and that many tumour types were not included in regulatory filings, post-marketing clinical trials are essential to gather more information on the full spectrum of drug activity.

The largest histology agnostic trial to date has been the NCI-MATCH trial that enrolled some 6000 patients in the USA. After fresh tumour biopsies assessing a panel of genes, patients with tumours expressing actionable genes, were treated with drugs matched to those genes. Unfortunately, response rates observed in the study have been disappointing (htpps://ecog-acrin.org/nci-match-eay131-findings). The reasons for this have not yet been determined but there are various challenges related to such trials: small sample sizes, wide confidence intervals, unequal responsiveness of tumours, difference in biomarker prevalence and predictive value, standardization of the molecular diagnostic tests, lack of control groups, and many more.

In drug-repurposing, ASCO launched its Targeted Agent and Profiling Utilization Registry (TAPUR) Study in 2016 to study the efficacy of marketed, targeted drugs used to treat patients with solid tumours that harbor a molecular alteration known to be a drug target. To date nearly 2100 patients have been treated and results have been reported for several study cohorts that have the potential to extend the use of approved drugs to new populations. A summary of study results is available at https://www.tapur.org/news.

Regional Matters on the Road to Global Approvals

Irmela Radtke (Roche, CH)

Timely global approvals are an important milestone to enable patient access to innovative treatments. During the COVID-19 pandemic, this common goal becomes much more tangible when vaccine approvals come in with different regulatory procedures and schedules in different regions to add to the amatory to fight the pandemic. In oncology drug development with smaller patient populations, a diverse and rich treatment landscape, regional matters are much more pronounced. The ICH landscape focusing on ICH E5 R1 «Ethnic Factors in the acceptability of foreign data», the associated Q&A from 2006 and the ICH E17 “General

principles for planning and design of multi-regional clinical trials" describes important concepts to achieve global approvals. Largely the framework on ethnic factors outlined back in 1998 in E5, still holds true. The Avastin & Tarceva case study from 2016 describes many global approvals in "first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor activating mutations", based on Japanese pivotal data. This case study illustrates, that bridging according to ICH E5 framework can be done successfully but also that early engagement with regulators on the proposed package is advisable and feedback on the proposal can vary. Looking forward, the deeper and more complete insights of "inclusive research" into ethnic factors from recent years are important, as many references show, e.g. [Ref 1-3]. The nature and impact of the combination of extrinsic and intrinsic factors for clinical development needs to be understood much better in this context. It is concluded that study designs will keep evolving and together with new technologies and an inclusive research approach, regional matters on the road to global approvals can be addressed.

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Regulatory Perspective on Cancer Drug Development in a Global Setting

R. Angelo de Claro (FDA, USA)

Even during the COVID-19 pandemic, FDA Oncology Center of Excellence (OCE) has remained highly active on several initiatives consistent with its mission to advance patient-centred regulatory decision-making through innovation and collaboration. Project Orbis, a global collaborative program launched in 2019, reported 38 approvals in its first year. Current Project Orbis partners include the regulatory health authorities of Australia, Brazil, Canada, Singapore, Switzerland, and the United Kingdom. FDA OCE reported the initial experience with the Real-Time Oncology Review (RTOR) program which facilitates earlier submission of datasets to support an earlier start to the FDA application review. The median approval time was 3.3 months (range 0.4-5.9 months) for the initial set of 20 marketing applications that used RTOR (February 2018 to April 2020). Other regulatory achievements include the issuance of 17 guidance in 2020 on many aspects of oncology drug development, including the broadening of eligibility criteria for cancer clinical trials. Patient-centred efforts include Project Community which introduces the work of the FDA to underserved communities and Project Facilitate which is a single point of contact call centre to health care providers through the expanded access request process. To facilitate interactions across multiple programs, OCE switched to virtual platforms to continue the attention on cancer drug development and to assure patients with cancer that they have not been forgotten.

Q&A and Discussion:

- It is yet unclear if there is a threshold of prevalence of SNP's that would lead to forced SNP based dosing in populations.
- Likely germline polymorphisms will also influence exposures to targeted TKI's and IO drugs. For oral drugs, absorption related polymorphisms may be an added challenge.
- To enable design of a global pivotal trial, the basic consequences as mentioned before, in the various ethnicities, will have to be known. Both for marketing approvals, as well as for HTA.
- The relevance of different tumour-mutations seems to be variable throughout tumour types, in their response to targeted agents.
- Most RTOR related approvals were on drugs that had a Breakthrough designation. Planning of starting an RTOR trajectory will need a timely discussion with the regulator.
- For solidity of data in a tumour agnostic setting, it is recommended that there is a certain pre-set number of patients in a responding population. Particularly to facilitate the HTA process. Conditionality could be part of a positive HTA opinion, so the condition to collect more data after reimbursement approval.
- If tumour agnostic approvals become more common, the total cancer population will have to be genetically tested. We need to ask the question if the costs related to this testing, are acceptable from an HTA perspective as well.
- For Project Orbis, FDA noted that each participating country retains full independence on the final regulatory decision. FDA coordinates the meetings between the regulatory authorities.
- FDA is actively looking at the effects of the COVID-19 pandemic on the conduct of cancer clinical trials. FDA had issued guidance documents for industry, investigators, and institutional review boards.

SESSION 4 – ADVANCES IN IMAGING

Radiology Imaging

Marion Smits (Erasmus MC, NL)

The level of radiological imaging can be divided into three pillars of increasing complexity: for clinical trials, for specialist medical centres, and in the context of imaging research (the 'imaging laboratory'). The current level of imaging and image assessment in the context of clinical trials is extremely basic, which means that both patient selection and response assessment based on imaging are currently suboptimal. Various reasons for this can be identified, including lack of involvement of imaging experts in the conceptualization and implementation of trials, lack of funding, and the fact that recruiting centres may not be optimally equipped from an imaging perspective.

Even so, various more advanced imaging techniques, such as diffusion weighted imaging (providing a measure of tissue cellularity) and perfusion imaging (providing quantitative values of tissue perfusion) are current standard of care and have great potential to improve outcome assessment in the clinical trial context as well as provide further insights into tumour biology and pathophysiology.

The latter aspects are the focus of imaging research, where novel techniques allow non-invasive assessment of tissues at the molecular level. One such technique is chemical exchange saturation transfer (CEST) MRI, which allows the visualization and – to a certain extent – quantification of macromolecules, including various proteins and glucose. Experimental studies indicate the potential of such techniques to provide true imaging biomarkers of disease activity. Inclusion of such techniques into clinical trials would boost their development while at the same time providing invaluable insights into tumour biology in response to treatment.

Molecular Imaging

Wim J.G. Oyen (Humanitas University and Humanitas Clinical and Research Center, Milan, Italy; Rijnstate Hospital, Arnhem, The Netherlands)

Over the past decades, molecular imaging has advanced considerably. In molecular imaging, targeted molecules are tagged with a label, radioactive for PET/CT and SPECT/CT or fluorescent/bioluminescent for optical imaging, to allow assessment and often also quantification of specific features of cancer cells or the tumour microenvironment.

Besides the use of molecular imaging for staging and restaging of cancer patients, depicting heterogeneity in expression and modulation of targets on cancer cells (within tumours and between metastases) has become an important area of research, yielding highly promising preliminary results in e.g., breast cancer and prostate cancer. For drug development, molecular is a very useful and sometimes essential tool to establish a rational dosing regimen and to assess the impact of a combination of drugs. While in the latter, the research questions are the most relevant, the pivotal question when translating novel imaging technology to clinical practice is the impact these modalities have on patient management (e.g., change of therapy, predictive and prognostic value). Whatever the indication for including molecular

imaging into research protocols or clinical practice, rigorous methodology, standardisation, and quality control are of the utmost importance. When that has been established, inclusion of advanced imaging in early clinical trials is necessary to generate the required evidence to define the utility for its larger scale use.

Q&A and Discussion

- Both lectures indicated we do not make maximal use of the available novel technologies. How can we advance new imaging techniques to be used toward product approval, i.e., in clinical trials?
    - Imaging is used as a biomarker. And there we rely too much on tradition.
    - Consensus in the field is important but can only come after validation.
    - Lack of (the often laborious) validation on biology, as well as clinical perspective, is an issue. Including standardization, and the development of imaging protocols. These have their own cost concerns.
    - Actively involve imaging experts, at the earliest point of clinical development, and select the imaging technology that provides the best information, with focus on patient-selection for treatment, and patient benefit of that treatment. That could also take away the discussion on costs of imaging since imaging as a selection biomarker can help avoid useless treatment. And imaging costs in the end will be negligible in the overall costs of treatment.
- What is regulatory acceptance of new imaging techniques?
    - A not yet formally validated technique will likely not be acceptable from a regulatory perspective.
    - Appropriately selected imaging will have true value for health technology assessment.
    - The European Society of Radiology provides some guidelines for imaging biomarkers, that are also used by the EMA (Imaging Biomarker Alliance).
- There is no imaging technology that serves every single purpose. One needs to know what one is looking for, when selecting the technology.

SESSION 5 – REGULATORY HOT TOPICS

Patient preferences

Hans Hillege (CHMP; EMA, NL)

Over the last few years, there is a move toward including patients' values and perspectives in regulatory decision making and there is a growing acceptance that the trade-off made by patients differ from those of clinical experts. Methods to capture the views of patients are under intense investigation to assess the feasibility and reliability of the data gained by these methods.

The challenges for public involvement within the regulatory environment are multifold;

- definition of who represents the patient voice.
- by what means/methods can the patients' views be reliably collected.
- at what point in the decision process should patients' views be integrated.

Regardless of the type of involvement, decision-makers and patient advocates should rely on validated studies to inform them about the trade-offs of patients are willing to make.

Preference information from decision-makers may assist decision-makers in taking complex decisions. It will help decision makers make value trade-off explicit, facilitate clear thinking about the problem, and make decisions easier to communicate. The Center for Devices and Radiological Health of the FDA issued a guidance of where patient's preference fit with other patient experience data, starting with patient input, and involving patient perspectives and patient reported outcomes (https://www.fda.gov/media/92593/down).

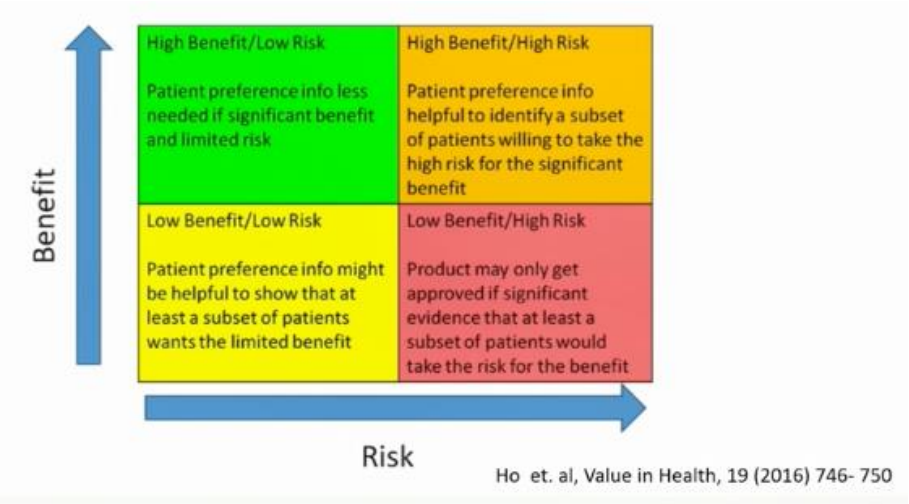
Preference information's (**PPI**) are qualitative or quantitative assessments of the relative desirability or acceptability to patients, of specified alternatives or choices among outcomes or other attributes that differ among health intervention alternatives. They describe what patients do value, and what they want.

Patient reported outcomes (**PRO**) are reports of the status of a patient's health condition that come directly from the patient, without interpretation of this status by a healthcare professional.

PPI's can numerically be expressed on a utility-desirability scale in a benefit/risk assessment. PPI's elucidated from patients can help in situations of a combination of high benefit (progression-free survival) and high risk (for instance Grade 3-4, severe or life-threatening toxicity) indicating which patients are willing to accept the high risk because it outweighs the current benefit of existing therapies with their characteristics. So when comparing Utility values, an assessment op patient preference can be made.

There are 4 preference elicitation methods (Drug Discovery Today, vol. 24, nr 7, July 2019): Discrete choice methods, Ranking methods, Indifference methods and Rating methods. Discrete choice methods are most frequently used and allow the evaluation of multiple attributes at the same time.

In different situations PPI be different levels of help to the regulator, in guiding complex decision making, as outline in the graph.



Patient derived data generate information about the impacts, burden of disease and treatment, how to better integrate and communicate the information of outcome data into benefit risk assessments, to health care policymakers, prescribers and patients.

Q&A and Discussion

- Who are the patients that we are seeking this information from?
  - Unbiased information is crucial.
  - Large data sets are important to reduce bias.
  - Patient advocates and patients' representatives are not those that should provide information on patient preferences.
- Industry involves patients early in clinical trial design. Should they also be involved in regulatory design?
  - There is indeed contact with patients.
  - Early collection of data is important. But there are some situations where the benefit is so obvious that patient data would not have to be collected. So, we need to balance this against the cases where the information was key.
  - There is no best approach to this.
- How can patient preferences be included in trial design discussions, and how could they be included in the discussions in Scientific Advice?
  - If high risk is expected (alongside high benefit,) then including patient preference ins Scientific Advice seems key.
  - It is important to realize that patients with diseases that create high risk, are willing to accept more risk in safety of drugs. Particularly for the early stages of development the relevance of achievements for patients, are more important than the issues of regulators.
  - In the post-authorization phase, there is also a need to assess patient preference information.
- Which congresses or information sources could also help to gain insights in the methodologies involved in PPI?
  - ISPOR (International Society for Pharmacoeconomics and Outcome Research)

- Disease oriented conferences
- Outputs from the IMI project "Prefer" (https://www.imi.europa.eu/projects-results/project-factsheets/prefer).

RWE: technical perspective

Sinan Bardakci Sarac (DKMA, DK)

For decades, the Randomised Controlled Trial (RCT) has been considered the gold standard for data generation. ICH-E10 states that "the inability to control bias is the major and well-recognized limitation of externally controlled trials and is sufficient in many cases to make the design unsuitable". This seems to argue against the increasing interest among drug developers to use external controls based on real world data (RWD). So, the question is if ECH-E10 is overly cautious?

In the RCT there is matching for patients and controls, which allow adjustments for measured confounder. ICH-E10 states that "matching on selection criteria or adjustments made to account for population differences, should be specified prior to selection of the control and performance of the study. Therefore, for external control groups from RWD to be acceptable for regulatory decisions, it should be clear that the outcomes in both arms of the study were unknown when the external controls were selected. So, the decision to use an external control arm should be specified prospectively.

A further challenge is posed by the fact that patients are selected for and enter the study- and the external control groups, through different mechanisms. This leads to missing key data in the external control arm, such as data on prognostic factors (in selection as well as survival). In the external control arm, there are no mechanisms for handling missing data. So, standardizing prospective data collection for outcome measures in patient registries, will be essential to expand their utility when generating valid RWD.

Also, a common baseline in both arms is crucial for time dependent endpoints such as survival, to ensure similarity in progression rate at study start. In addition, uniform methods for evaluation of treatment effect are crucial. In this respect, the sometime considerable difference between investigator review evaluation and blinded independent review evaluation, give rise to concern. In an external arm, post baseline treatment decisions, use of concomitant therapies and supportive care, cannot be, or are more difficultly, controlled.

In conclusion, analyses based on uncontrolled Real World data (RWD), should be based on validated methods for data collection and decision making, and only be used for critical regulatory decisions in the pre-approval setting, when there is sufficient evidence that such methods are robust and conventional development strategies have been considered.

At the moment, establishing efficacy based on RWD/RWE is not considered possible. Thus/currently, RWE/RWD cannot as such replace RCTs due to inherent limitations, which seem difficult to resolve with current methods.

Q&A and Discussion

- Ultimately, drugs are developed for use in the real world. Does the lecture suggest that yet RWD will be excluded from regulatory process? And what are the thought on using historical data from previously, or even contemporaneous, performed trials?
    - What is relevant is that the data are of good and reliable quality. Pre-planned collection of RWD registries, following a specific protocol and pre-discussed with the regulators, could be acceptable.
    - Indirect comparisons between trials remain difficult, and one tries to avoid this. And historical data would be hampered by the recent changes in cancer biology understanding.
- Would previously provided marketing authorisation be withdrawn by EMA, if RWD would not support the outcome of single arm trials?
    - Not very likely on efficacy data. But if safety concerns arise, this could indeed lead to active withdrawal marketing authorisation.
- Would RWD would be acceptable to use for an update the label or product information of an existing market authorisations, i.e., to fill existing gaps?
    - Yes, this is happening.
- Should sponsors wait for a Guidance on RWD?
    - RWD/RWE, if collected prospectively in the right way, can have value for regulators. This is much more difficult for retrospectively collected RWD.
    - There is a draft guideline of the EMA on the frame of registry-based studies, that is currently in public consultation.
    - If the use of RWD is considered for a dossier submission, prior consultation of the Scientific Advice Working Party or the Innovation Task Force, is strongly recommended.
    - The latter also holds for patient groups that intend to provide registries.
- What are the key points of concern on RWD/RWE?
    - The reason why patients enter a study, or not, could lead to totally different populations. The way of collection of the data is the second major concern.
- Should clinical trial protocols not be more reflective of Real World need?
    - This could be done in a relatively large RCT. In smaller and smaller single arm studies, this will be increasingly difficult. In the latter scenario, a good quality small study in a homogeneous population, supported by the above-described good quality prospectively collected RWD, would be preferred.
    - The trials, if possible, should be closer the real world need, by involving more study sites.
- To what extent could RWE compensate for an inconclusive prospective trial?
    - This is unlikely to happen. The trial assessment would remain leading. RWE will not become pivotal evidence for a marketing authorisation.
- Can RWE be used to guide the design of prospective clinical trials.
    - Yes, but the quality of the RWE, is very important in considering this. Poor quality RWE would still not lead to good quality RCT's.
- Could RWD resolve some of the issues in prospective trials with missing data, or missing power, due to the COVID-19 pandemic?

- This is difficult to answer in a black and white way.

Fireside Chat

John Smyth, Ralf Herold, Hans Hillege, Sinan Sarac, Ruth Plummer, Judith Taylor, Claudia Hey

- The multi-stakeholder set-up is considered as one of the assets of CDDF meetings.
- The active involvement of the patient voice, and the patient-centred approach, are much appreciated. The patient voice is becoming more educated and influential. Continued training of patient advocates will be incredibly important. There was a CDDF workshop in 2019, on patient involvement. And repeat something similar in 2022, was suggested. This could include aspects of the IMI “Prefer”-project.
- Tumour agnostic aspects will be centre a lot of future activities. Despite the failure of the NCI-MATCH study.
- Real time oncology review (FDA-RTOR) was enthusiastically welcomed. Lessons can also be learned from the rolling reviews of COVID-vaccine trials.
- The development of a Forum to discuss unequal access to drugs, received a lot of support.
- The EU beats cancer plan was mentioned as one potentially important framework for such a discussion.