



Summary of Discussion

**Cancer Drug Development Forum (CDDF)
Multi-Stakeholder Workshop**

The Use of Real-World Data to Optimize Oncology Drug Development and Access

21–22 November 2019
Amsterdam, Netherlands

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PROGRAMME

Day 1 Thursday 21 November 2019

13:00 **Welcome note**
John Smyth (CDDF Board, UK)

13:15 **Overview of the current RWD landscape**
Nafsika Kronidou Horst (Roche, CH)

SESSION 1: THE CURRENT POSITION AND KEY CHALLENGES

Chairs: *John Smyth (CDDF, UK) and Nafsika Kronidou Horst (Roche, CH)*

Regulators' and Payers' Perspective

13:30 **European Medicines Agency**
Ralf Herold (EMA, NL)

13:50 **Health Technology Assessment**
Carin Uyl-de Groot (Erasmus University Rotterdam, NL)

14:10 **Q&A session/Discussion (10 min)**

Clinician's perspective and industry case studies

14:20 **Clinician's perspective on RWD repositories**
Jaap Verweij (Erasmus University Rotterdam/CDDF, NL)

14:40 **Industry case study 1: real-world comparator in a single-arm study**
Valérie André (Eli Lilly, FR)

14:50 **Industry case study 2: a pan-cancer registry proposal**
Marlene Thomas (Roche, CH)

Patient Perspective

15:00 **Patient perspective**
Roger Wilson (UK)

15:10 **Coffee break (20 min)**

SESSION 2: METHODOLOGICAL ISSUES

Chairs: *Eva Skovlund (Norwegian University of Science and Technology, NO) and Ralf Herold (EMA, NL)*

15:30 **Introduction to methodological challenges**
Eva Skovlund (Norwegian University of Science and Technology, NO)

DATA COLLECTION

- 15:35** **Disease-based registries**
Espen Enerly (Cancer Registry of Norway, NO)
- 16:05** **Product-based registries**
Elmar Schmitt (Merck Healthcare KGaA, DE)
- 16:30** **Wearables and patient-reported outcomes: new wins?**
Cécile Ollivier (Aparito, NL)
- 16:55** **Q&A session/Discussion (15 min)**

DATA ANALYSIS

- 17:10** **Statistical considerations in building external control**
Chris Harbron (Roche, UK)
- 17:35** **Electronic health records**
Meghna Samant (Flatiron Health, USA)
- 18:00** **Introduction of breakout sessions (30 min)**

Day 2 Friday 22 November 2019

SESSION 3: IDENTIFYING SOLUTIONS - BREAKOUT SESSIONS

- 09:00** **Identifying solutions – 4 breakout sessions**
Breakout session 1: regulatory and HTA environment for the use of RWE
Chairs: Stefan Schwach (Lilly, UK) and Nafsika Kronidou (Roche, Basel)
- Combined breakout sessions 2 and 4: patient voice and data-collection systems
Chairs: Roger Wilson (UK), Irmela Radtke (Roche, CH), Meghna Samant (Flatiron Health, US), and Bjørge Bolstad (Norwegian Medicines Agency, NO)
- Breakout session 3: ensuring robust decision making from the analysis of RWD
Chairs: Chris Harbron (Roche, UK) and Eva Skovlund (Norwegian University of Science and Technology, NO)
- 11:00** **Coffee break**
- 11:30** **Consolidating outcomes from breakout sessions**
- 12:30** **Wrap-up and next steps**
John Smyth (CDDF, UK)
- 13:00** **Lunch (I-Dock restaurant, Room Mate)**

EXECUTIVE SUMMARY

While randomized controlled trials (RCTs) remain the gold standard, real-world data (RWD) can play an important role as a source of supplementary evidence, i.e. real-world evidence (RWE), for healthcare decision making. Driven by the availability of new technologies that enable the collection of large volumes of healthcare data and methods to analyse and link the data, RWD is a rapidly evolving field with increasing global focus from regulatory, health technology assessment (HTA), academic, healthcare professional, patient, and life sciences industry perspectives.

The goal of this multi-stakeholder meeting was to identify key challenges in RWD proposals facilitating healthcare decision making in oncology, to share experiences, and to discuss methodological issues for obtaining RWE that is fit for regulatory decision-making and access. Issues concerning RWD quality, quantity, ownership, and privacy were discussed. This meeting expanded on a previous [Cancer Drug Development Forum \(CDDF\) discussion](#), reflecting the rapid advancements in the field.

Despite increased interest, there is a lack of understanding of how RWD/RWE can be leveraged in a transparent, reproducible, and principled way to generate additional or novel insights. Moreover, clinicians and patients struggle with a lack of clear definitions for RWD/RWE and meaningful endpoints, such as overall survival and quality of life, which are not readily retrievable in some RWE data sets. Overall, there is a need to establish new methods and study designs for real-world study conduct.

Breakout sessions that aimed to identify potential solutions to the existing challenges highlighted the importance of prospective RWD collection using the appropriate methodology to minimize biases in addition to the role of cancer registries in collecting robust RWD. The involvement of patients as key stakeholders was identified as being critical to ensuring increased value for patients. Harmonization of data collection approaches (e.g. common data models) and the need to identify global solutions beyond the EU or country level while complying with the General Data Protection Regulation (GDPR) and national legislations were emphasized.

INTRODUCTION

Overview of the current RWD landscape

Nafsika Kronidou Horst (Roche, CH)

Although randomized controlled trials (RCTs) are the best way to establish causal inference, they have some limitations. RCTs may not reflect the “real-world (RW)” population as they are essentially an experiment in a model population: they occur within a limited time frame, capture information from a limited number of patients, and often are not large enough to detect rare treatment effects. Moreover, in oncology it is not always ethical to have patients on placebo or a potentially inferior standard of care (SOC), or sample sizes might be too small to power trials sufficiently due to low prevalence of rare cancers. While RCTs remain the gold standard, real-world data (RWD) can play an important role as sources of supplementary evidence for regulatory/health technology assessment (HTA) decision making.

The European Medicines Agency (EMA) and US Food and Drug Administration (FDA) have developed similar definitions for RWD:

EMA working definition: *Routinely collected data relating to a patient's health status or the delivery of healthcare from a variety of sources **other than traditional clinical trials***

FDA definition: *Data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources*

These definitions are intentionally broad to accommodate the rapidly evolving new technologies (e.g. electronic health records [EHR], claims databases) and novel settings (e.g. wearable technology, social media, large clinically annotated genomic data sets, and product/disease registries). Real-world evidence (RWE) is the evidence derived from the analysis and/or synthesis of RWD.

Leveraging RWD/RWE as an evidence base to support healthcare decision making is of interest to all healthcare stakeholders, including healthcare professionals (HCPs; to improve clinical treatment decisions), patients (to facilitate conversations with their treating physicians and to improve outcomes), industry (to inform product development and meet unmet medical needs), regulatory agencies (to protect public health), academia (to inform research), and HTAs and payers (to inform reimbursement decisions and measure improved health outcomes).

Considerations for RWD quality and relevancy for regulatory purposes have been published in a [White Paper by the Duke-Margolis Center for Health Policy \(Durham, NC, USA\)](#). According to that paper, generating RWE fit for regulatory approvals should focus on matching the strength of the available RWD sources and study methods to the specific regulatory and clinical context. This results in leveraging different types of RWE.

Globally, regulatory agencies are engaging in multi-stakeholder discussions through workshops and research projects to better understand how to leverage RWE for regulatory decision making. For example, the FDA published a [framework for their RWE programme](#) in December 2018, and is developing draft guidance on the use of RWE, which is expected by 2021. The EMA and national agencies in Europe are also exploring how to leverage RWD. Several EU initiatives are underway, including: 1) [Patient Registry Initiative \(Good Registry Practice\)](#); 2) [EMA/HMA Big Data Task Force](#); and 3) [RWD ecosystem based on a common data model to create “a learning healthcare system”](#) .

RWE has the potential to transform how we undertake drug development. Challenges and potential solutions related to the generation of relevant and high-quality data, tools, and methods to analyse the data and appropriate study design were the subject of the subsequent discussions within the workshop with a clear intention to collaborate and identify global solutions.

SESSION 1: THE CURRENT POSITION AND KEY CHALLENGES

European Medicines Agency

Ralf Herold (EMA, NL)

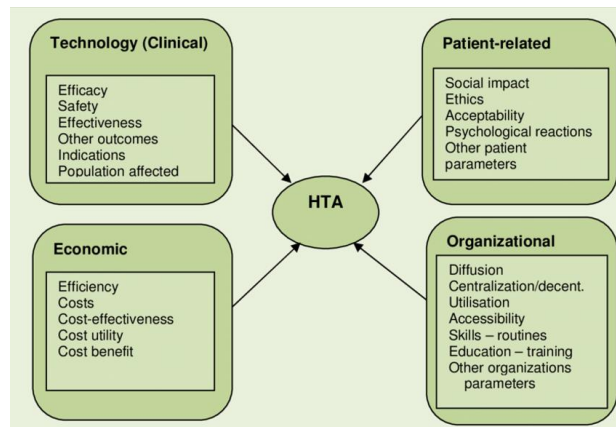
To enhance regulatory science, clinical-evidence generation needs to evolve further with innovative clinical trial methodologies, small target populations ideally defined by molecular markers, novel incidentally collected data sets (“RWD”), and the capability to perform non-traditional analyses such as Monte Carlo methods and probabilistic statistical inference in large data sets. Besides RWD/RWE, other EMA activities include adoption of new trial designs; integration of patient-reported outcomes (PROs)/clinical outcome assessments; making use of accelerated and conditional pathways of decision making, as well as the use of complementary RWD data sets to strengthen the totality of evidence. A range of novel, non-RCT analytical methodologies have been proposed, e.g. construction of external control data,

reweighing of RCTs to reflect real-life, etc. However, to be accepted by decision makers, such RWD/RWE approaches should be developed according to a pre-agreed plan, as a development exercise that is separate from the drug development process itself. Sponsors are advised to seek scientific advice on RWD proposals, and in addition, to make use of the methodology qualification procedure, a process which includes public consultation. While inductive inference is used for experimental data (such as from RCTs), incidentally collected data, such as RWD, require understanding as well as generating a model (such as treatment courses in the RW). Using RWE as clinical evidence means to adapt principles for transparency, replicability of methods, and reproducibility of results.

Health Technology Assessment

Carin Uyl-de Groot (Erasmus University Rotterdam, NL)

HTA is a process of systemic evaluation of the technological (clinical), economic, patient-related, and organizational aspects of a health technology with the purpose to inform policy decision making (Figure), including reimbursement and clinical guidelines.



While healthcare budgets increase by 1.2% per year, costs are raising exponentially with the introduction of new and expensive medicines and technologies. Healthcare budgets are faced with the challenge of opportunity cost, e.g. what we give to patient A we cannot give to patient B, and the need to make a societal decision on the affordability of care. Currently, there are several value-based pricing models. These include using a cost per quality-adjusted life-year (QALY) threshold (e.g. National Institute for Health and Care Excellence [NICE]: GBP 30,000); pay for performance (i.e. treatment success); or volume price arrangements.

As cost containment becomes crucial, there is an increased demand for robust evidence. RWE is lower in the hierarchy of evidence as it does not allow us to make causal inferences. However, RWE complements the RCT data by providing information on patients and treatment heterogeneity in clinical practice. For example, [an analysis of 1,524 patients with castration-resistant prostate cancer \(CRPC\) from a Dutch registry](#) indicated that patients treated on clinical trials were younger and had fewer comorbidities than those not treated on clinical trials; the observed survival advantage in the first group was not retained after adjusting for baseline characteristics. Thus, external validity of RCT results is very important for HTA evaluation.

RWE is expected to become more important in pricing and reimbursement decisions in rare cancers as medicine becomes more personalized. Oncology patients go through multiple lines of therapy and RWE can provide valuable information in addition to RCTs to inform disease modelling on the most optimal treatment sequence from both a clinical and economic perspective. Additional opportunities for RWE include information on patient access to new therapies, adherence, revised indications, guiding RCT design, and post-marketing assessment of safety and effectiveness. In all cases, matching the study objective with the methodology, and clear communication on patient characteristics, treatment, and outcome parameters, is paramount for contextualizing the data and understanding their limitations.

Discussion

- The CRPC registry experience provides a strong rationale for designing RCTs that are more representative of the RW population.
- Currently, QALYs are the best measure of cost–benefit, and they can be compared easily across studies. Other instruments, such as the European Organisation for Research and Treatment of Cancer core quality-of-life questionnaire (EORTC-QLQ-C30) or other disease-specific tools, provide supplementary information for utility assessment.
- Pragmatic clinical trials realized by relaxing the selection criteria of RCTs are an acceptable means to exploit RWD that could suit the needs of HTA bodies.

- Attrition bias can explain some of the treatment effects seen in RCTs, therefore results should always be confirmed by RWE.
- Identifying the subset of patients that is most likely to benefit from a certain drug is important to contain the cost of care as we are treating a large proportion of patients without any benefit or with only marginal benefit.
- The issue of selection bias is an important issue in RWD, especially in the case of unstructured data. In addition, the global nature of many diseases requires a representative sample to be obtained; failure to do so is a source of bias.

Clinician's perspective on RWD repositories

Jaap Verweij (Erasmus University Rotterdam/CDDF, NL)

Precision medicine offers opportunities for patients, however the complexity and volume of information is increasing rapidly and can be overwhelming for oncologists. For example, histological classification of soft tissue sarcomas identifies 56 unique histological types, and further subtyping at the molecular level identifies 62,000 mutations. In non-small-cell lung cancer (NSCLC), patients with gain-of-function epidermal growth factor receptor (EGFR) mutations show a high rate of response to EGFR tyrosine kinase inhibitors, whereas patients whose tumours are refractory to that treatment do not harbour these mutations, highlighting the importance of patient selection for targeted therapy.

The goal of clinicians is to prescribe the right treatment for the right patient at the right time. Budget considerations affect these decisions, as clinicians need to follow clinical practice guidelines in order to obtain reimbursement. RWD can help inform treatment decisions, but there are no readily available solutions; this situation is further complicated by inconsistency in definitions. Hospital data repositories can be used to generate RWD on adherence to clinical protocols as well as serve as sources of research. Some of the limitations of these repositories include data quality and consistency concerns as data input is mostly done by practice assistants. Of note, across available platforms, safety and dosing information is not yet recorded consistently and might be partly unreliable, but the platforms are already generating research output and are expected to have a positive impact on outcomes. In this context, it is also worth mentioning the [Google–Ascension](#) collaboration using Google's digital technology



to analyse patient records for Ascension, which with over 2,500 centres is the largest not-for-profit US health system. However, criticism of data privacy is one of the challenges this project is facing.

From a clinician’s perspective, [there is value in RWE](#) as it complements outcomes from RCTs and provides supportive evidence to inform clinical decision making. However, building RWD repositories is challenging. To optimize its use in oncology, there needs to be clear definitions for RWD and RWE, simplified administrative procedures, and guidance on data entry, privacy, quality, and completeness.

Industry case study 1: real-world comparator in a single-arm study

Valérie André (Eli Lilly, FR)

There is a broad range of uses for RWD in clinical studies. RWD can inform trial design, site selection, enrolment criteria, and feasibility of traditional RCTs. Furthermore, trials in the clinical practice setting rely on RWD and include pragmatic trials and use of external controls. This case study discusses the addition of an external control in a single-arm, phase 2 study of cyclin-dependant kinase (CDK) 4/6 inhibitor in patients with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer. The objective of the comparison was to contextualize the efficacy results of the trial using a RW cohort of patients receiving single-agent chemotherapy from the Flatiron Health database (15,000 patients). The primary limitation of using external controls is selection bias based on differences in distribution of baseline characteristics. Patients were matched on baseline characteristics using Mahalanobis distance matching; sensitivity analyses were also performed to control for baseline differences. After using the selection criteria as well as analytical approaches, 108 patients from the trial were matched based on patient and disease characteristics to the same number of RW patients from the Flatiron Health database. The efficacy analysis showed a significant 46% reduction in the risk of death (hazard ratio = 0.536; $p = 0.0006$) for patients receiving CDK 4/6 inhibitor in the trial. A limitation of the analysis was that the cohorts were not contemporaneous, suggesting that the results are confounded by the availability of treatment options in the RW cohort (e.g. 31.5% of patients received CDK4/6 inhibitor following discontinuation of the index therapy).

This case study demonstrates that advances in statistical analyses and improvements in data quality enable the use of a RW cohort as an external comparator arm. Planning RW studies prospectively can help to address some of the challenges encountered in this case study.

Industry case study 2: a pan-cancer registry proposal

Marlene Thomas (Roche, CH)

Advanced diagnostics, such as next-generation sequencing (NGS), have the potential to improve outcomes for patients by selecting them based on genomic profiling for molecularly targeted therapy. Most genomic alterations are rare and not exclusive to a specific tumour



type. For instance, the average prevalence of *neurotrophic receptor tyrosine kinase 1 (NTRK1)* fusions is 0.0002–1.5% across various cancers and they seem to be more prevalent in rare cancers such as thyroid cancer and secretory carcinoma of the salivary gland (> 75% of cases). This rare prevalence poses a significant challenge for evidence-based decision making, as generating large RCT data in this setting is challenging. To identify 900 *NTRK*-fusion-positive patients based on a prevalence of 0.3%, 300,000 cancer patients would need to be screened. Therefore, supplementary data sources such as RWD are needed to understand patient characteristics and treatment effectiveness.

Molecular tumour boards (MTBs) are multidisciplinary platforms exploring off-label targeted therapy for specific genomic alterations common across cancer types. A case in point is a patient with a high level of mesenchymal–epithelial transition (MET) amplification and adenocarcinoma with unknown primary who had a response duration with crizotinib of > 19 months. Thus, MTBs are generating data that can be used to match patients to molecularly targeted therapy outside of approved indications. However, currently, these clinical practice data are not collected systematically.

Adaptive precision medicine trial designs are rapidly changing the treatment paradigm for patients with rare subtypes of cancers. The Drug Rediscovery Protocol ([DRUP](#)) enrolls patients in multiple, parallel cohorts (baskets) based on actionable genomic alterations by available targeted therapy and monitors response based on stringent criteria (complete response, partial response, stable disease \geq 16 weeks); patient cohorts are expanded if a response is observed. Preliminary results from DRUP indicated that 34% of 215 patients across 76 treatment cohorts experienced clinical benefit with a median duration of 9 months. Early progression-free survival (PFS) and overall survival (OS) data were also promising. Moreover, data from this academic study constitute a publicly available data repository for future analysis.

[Many clinical, access, and policy questions are best addressed using RWD.](#) One of the greatest strengths of RWD is the ability to improve the generalizability of conclusions from clinical research and to contribute knowledge by enabling the study of larger cohorts and/or by allowing longer periods of follow-up than typically used in RCTs. Clinico-genomic databases (examples include the Flatiron Health database of EHRs of patients with NSCLC) can yield clinically meaningful information on the association between genomic diagnostic results and



outcome. Currently, Roche is exploring the opportunity to establish a multi-stakeholder, prospective, pan-cancer registry capturing genomic NGS data linked to longitudinal patient outcome regardless of cancer type or stage, and treatment.

Patient perspective

Roger Wilson (UK)

Patients are looking for better treatments, better information, and better, more meaningful outcomes. While data availability leads to information and knowledge, it does not always mean that the patient can understand it as patients' abilities to understand this information varies greatly. Poor-quality information on drug risks/benefits can be deceiving to patients and can support risk-taking. There are numerous examples in the literature indicating that small phase 2 clinical trials fail to generate high-quality data, i.e. surrogate endpoints, such as PFS, often do not translate to an OS benefit or improved patient experience. In this context, RWD can provide robust and long-term data to inform individual decision making. Patients must be routinely involved in developing RWD studies to make such studies relevant. Studies designed to optimize treatment approaches, i.e. optimal combinations or therapy sequencing are of great importance to patients; [the EORTC proposals for treatment optimisation](#) could establish important standards in this regard. Patients' experiences on treatment are an essential element of drug value, and the need to capture PROs in longitudinal studies was emphasized. In addition, narrative medicine is a growing field utilizing social media mining tools to capture patient journeys. Finally, patients should also be consulted on communicating study results to their patient peers to further facilitate understanding.

Taken together, rigorous science with meaningful endpoints of OS and quality of life (QoL) should be at the core of patient-focused research. These endpoints deliver understanding and can improve outcomes for the individual patient.

SESSION 2: METHODOLOGICAL ISSUES

As an introduction to the session, Prof. Eva Skovlund highlighted the importance of observational studies in providing valuable additional information to RCTs. Drug approval is often based on only one pivotal trial. At the time of licencing, knowledge about the true risk-benefit balance is often limited. Observational studies can provide large sample sizes to obtain a deeper understanding of efficacy and safety in the general population post-approval, and to study predictive biomarkers. Data quality considerations, bias, and confounding are some of



the caveats of RWD. This session provides an overview of RWD collection with a focus on methodological considerations and solutions.

Disease-based registries

Espen Enerly (Cancer Registry of Norway, NO)

Registries play an important role in the collection of observational data. The Cancer Registry of Norway (CRN) is one of the oldest national cancer registries. The reporting of cancer cases to the registry is mandatory and exempt from patient consent. The CRN reports national statistics on cancer incidence, prevalence, and survival. For the major cancer types, the national clinical quality registry – an extension to the CRN – collects additional information on the diagnostics methods, therapy, and follow-up period beyond the initial cancer diagnosis. The main goal is to evaluate and provide empirical evidence for improving the quality of care by monitoring adherence to clinical guidelines, and to identify regional differences. Data entries from multiple healthcare sources are tightly curated in-house to ensure completeness, validity, and accuracy, and the coding used adheres to international standards to ensure comparability.

Through collaboration with several pharmaceutical companies and the Norwegian Cancer Society, drug information beyond initial diagnosis is currently being added to the national clinical quality registry, to cover the full healthcare journey and treatment continuum and make this more relevant for HA/HTA. The INcreaSe Pharmaceutical REporting (INSPIRE) project captures data for all cancers; lung and breast cancer data will be the first to be curated and made available.

An example highlighting the role of the CRN in supporting regulatory decision making includes an extension of a phase 3 clinical study with RW post-approval commitments in order to address the long-term efficacy, safety, and immunogenicity of a human papilloma virus (HPV) vaccine. The importance of prospectively planning a feasible RWD collection from registries and clinical biobanks was also emphasized.

To further leverage its database, the CRN is currently exploring mapping the data in line with ongoing harmonization initiatives at a European level, e.g. European Health Data and Evidence



Network ([EHDEN](#)), and the Observational Medical Outcomes Partnership ([OMOP](#)) [Common data model](#).

Product-based registries

Elmar Schmitt (Merck Healthcare KGaA, DE)

Merkel cell carcinoma (MCC) is an extremely rare skin cancer with a dismal prognosis and limited treatment options. This case study of avelumab (Bavencio®) for MCC illustrated the evolution of RWD use as evidence for control of regulatory decision making in this setting of a rare cancer with high unmet medical need. The pivotal, single-arm trial (EMR100070-003 [JAVELIN Merkel 200]) assessed the efficacy (best overall response as the primary endpoint) and safety of avelumab monotherapy patients treated with ≥ 2 lines of therapy. The submission strategy was discussed with the health authorities on multiple occasions over 2 years in order to overcome the initial scepticism driven by the small numbers in the RWD and to agree on methodology. The goal was to establish a historical reference database as the only option to substantiate the sparse existing literature-based historical control data and to place the trial results in clinical context. Comparative quality-controlled retrospective RWD was used as a historic control (100070-Obs001). There were 2 cohorts: a US-based cohort, featuring EHR data from outpatient oncology practices across 19 states, and an EU cohort based on an MCC-specific registry in collaboration with the German Cancer Research Centre. Matching the baseline characteristics from the pivotal study resulted in a very low sample size (20 and 34 patients in the US and EU cohorts, respectively). Large differences in best overall response with chemotherapy were observed between the 2 historical cohorts suggesting regional effects. However, the data consistently described the poor outcomes with historical chemotherapy in terms of short response durations. A confirmatory, single-arm study of avelumab in first-line patients (EMR100070-003 Part B [JAVELIN Merkel 100]) demonstrated the long-lasting effect of the drug on duration of response as the most relevant endpoint. Finally, both agencies accepted the data – not for the label claims – but as supportive data on clinical context in the absence of well-controlled study results. This case study emphasizes the importance of engaging early with the regulators and planning the use of RWD as historical

controls prospectively, together with the clinical study protocol, ideally substantiated by RW epidemiological data.

Wearables and patient-reported outcomes: new wins?

Cécile Ollivier (Aparito, NL)

Currently, there is limited understanding of patient experiences outside of clinical visits. Digital health technology can offer continuous remote patient monitoring and help to address some of the existing knowledge gaps related to how patients feel and function, but also to the burden of disease on patients and their caregivers. It provides a unique opportunity to engage with patients, enhance disease understanding, and ultimately improve patient outcomes. Companies are beginning to adopt digital technologies as exploratory tools in clinical trials, creating the opportunity to collect more robust patient-centric data in oncology. Nevertheless, there are important regulatory points to consider in relation to the use of digital tools in clinical trials and routine clinical care, particularly the definition of the context of use. For clinical trials, regulatory pathways to discuss digital tools include the EMA [qualification procedure](#) and [scientific advice](#). Whilst qualification of oncology-specific PROs is lacking, PROs are increasingly being incorporated into the benefit–risk evaluation of cancer products. The EMA and FDA recently published regulatory guidelines; the EMA Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man, “[The use of patient-reported outcome \(PRO\) measures in oncology studies](#)”, was published in 2016, and the FDA updated their guidance “[Clinical Trials Endpoints for the Approval of Cancer Drugs and Biologics \(QoL, Physical functioning, patient and caregiver experience\) measures in oncology](#)” in December 2018.

There are multiple examples of the use of wearables in various diseases with positive feedback from patients, sponsors, and HCPs:

- Paediatric pulmonary arterial hypertension (PAH) is a rare disease with a high unmet medical need. As for many rare paediatric diseases, hurdles to clinical trials include logistical challenges and the preference for non-invasive endpoints. As a result, there is significant off-label use in children of medicines approved for adults, leading to

important gaps in knowledge on disease manifestation and progression, and clinical response to treatment in children with PAH. Solutions considered by the EMA, the FDA, and Health Canada involved introduction of non-invasive endpoints including activity measurements combined with PROs.

- A successful example of the EMA qualification of PROs in chronic obstructive pulmonary disease (COPD) was presented. In COPD, physical activity is a predictor of disease progression. There are available measures that are related to physical activity, but no targeted measure of all relevant aspects of physical activity existed in COPD. The PROactive Consortium was created as a multi-stakeholder effort leading to the development of an instrument qualified to monitor patient physical activity and assess the effect of treatment to support labelling claims.

When technology is used in clinical trials, it is recommended to run feasibility studies to test the validity and reliability of the technology before launching large-scale studies. A key success factor is the early-stage engagement of patients and HCPs to co-develop the tool. Of note, patients' capability to cope with the technology can vary and requires appropriate training and ongoing support. Importantly, the regulatory requirements must be anticipated as early as possible. As with any RWD, data privacy and protection are key.

Digital health is an exciting and rapidly evolving field, however wearable technology is underutilized in oncology. The oncology community have the optimal operational and clinical setting to use technology towards more a patient-centric system.

Discussion

- Wearable technology adds a different dimension to what the burden of disease means for patients.
- QoL and productivity data are not captured in registries, but are important in terms of patient care.
- INSPIRE brings all stakeholders together to plan and perform analyse and interpret the data, including the patient organizations, regulators, and HTA bodies. PROs are not currently captured but will be included in the future.

- RCTs are not always feasible. In such cases, it is important to seek scientific advice and engage in discussion with the relevant agencies on the best alternative approach to gather evidence.
- CRN provides a great example of well-designed registry. Agreement on core data elements for registries is needed in order to obtain harmonized, robust data. This is especially relevant in rare cancers where patient numbers are small.

Statistical considerations in building external control

Chris Harbron (Roche, UK)

RCTs are the gold standard in estimating treatment effects because they can show direct causality, i.e. differences in outcomes for a patient receiving different treatment regimens.

Randomization protects against bias at baseline and generally leads to unbiased treatment-effect estimates. Even with complete data, comparisons may be non-trivial and are complicated by factors related to the totality of patient experience, e.g. impact of rescue therapy, tolerability, QoL, etc.

In certain situations, RCTs can be unethical or impractical, i.e. no accepted SOC, paediatric indication, or rare diseases. In these situations, external controls might be an alternative to randomization. Using external controls in single-arm studies differs substantially from a randomized control because patients are not selected from a common pool in a controlled environment. Patients may be different as a result of patient selection, site selection (i.e. selection bias), different process of data capture (i.e. measurement bias), or regional differences in healthcare practices; this introduces a systemic bias and confounds the response distribution. Different techniques can be performed in order to create comparable sets of populations between 2 different data types. The first step is to apply the exclusion/inclusion criteria used in a clinical trial. This approach can be challenging with regard to missing data for patient selection and highlights the need to plan prospectively for both the clinical trial as well as the RWD analysis to account for such a challenge. One methodology is that of matching, i.e. selecting patients based on a direct one-to-one match with key characteristics between the 2 different groups. The caveat of this approach is that the distributions of the populations are changed from the original ones. Propensity scoring is

another approach that is being used increasingly. It uses known prognostic factors to weight external control patients to create a “study-like” population. However, this reweighting does not account for unmeasured confounders; it can also change the statistical behaviour of summary statistics and tests.

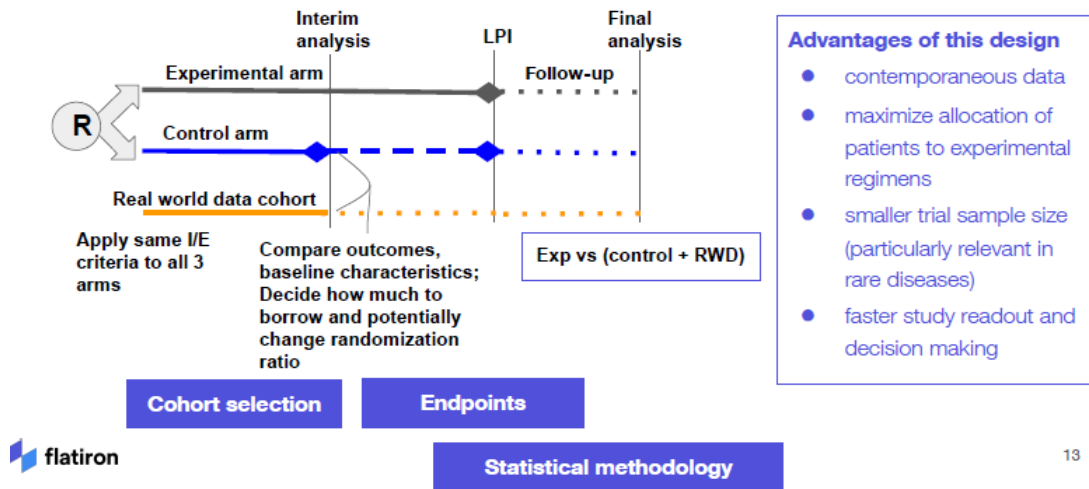
As with any RWD, data quality is paramount. For example, if mortality events in the control arm are missing, this will reduce the statistical power by making the control arm appear better. This can be mitigated by increasing the sensitivity through also considering additional data sources in identifying mortality events. There is a whole range of biases that can occur when using external controls, therefore these should be reserved for control situations where the natural disease course is robustly predictable. Careful prospective planning can help mitigate these biases and ensure robust RWD for regulatory purposes, such as supporting approvals, and HTA appraisals.

Electronic health records

Meghna Samant (Flatiron Health, USA)

Flatiron Health is a US health technology company. Flatiron Health’s proprietary EHR software, ONCOEMR, is deployed across 280 cancer clinics (> 800 unique sites of care) in the USA, allowing access to > 2.2 million patient records. In addition, Flatiron Health has forged alliances with large academic centres in the USA through “Flatiron for Academics”, which serves as an analytical platform for research purposes.

EHRs allow for continuous data aggregation from structured sources (e.g. diagnosis, lab, visits, therapeutics collected in a specific field on a form) and unstructured sources (e.g. free text in physician notes, specialist reports, etc.). About 60–70% of the data in oncology is unstructured. Both structured and unstructured data undergo processing and data quality controls, and, thereafter, are combined in longitudinal, RWE, disease-specific data sets for research. Linking enhanced clinical RWD patient data with external comprehensive genomic data, creates rich clinico-genomic databases for pan-tumour research and patient segmentation by genomic alteration or biomarker of interest (currently approx. 50,000 patients, and growing).



Hybrid controls using contemporaneous RWD cohorts represents a novel, and potentially more efficient, RCT design to supplement/augment the control arm. This approach maximizes patient allocation to the experimental arm when randomization is not feasible or not preferred (Figure). As previously discussed, RW patient cohorts should be representative of the population of interest, and require appropriate statistical methodologies to address missing data and mitigate potential biases. Selection of relevant endpoints is another important consideration to avoid assessment bias with OS being the most objective endpoint. Additional statistical considerations include statistical power and a realistic estimate of the uncertainty of the conclusions (type 1 error). Moreover, detailed documentation should be used to make the selection process transparent and traceable.

Use of hybrid controls can be particularly suited for certain clinical trial scenarios involving long enrolment timelines; feasible, but challenging randomization; stable SOC over time, and trials with OS as the primary endpoint (as OS is an objective endpoint). Altogether, EHR data have the potential to provide research/regulatory-grade evidence and complement evidence from clinical trials for decision making.

SESSION 3: IDENTIFYING SOLUTIONS – BREAKOUT SESSIONS

Breakout session 1: regulatory and HTA environment for the use of RWE

Chairs: Stefan Schwach (Lilly, UK) and Nafsika Kronidou (Roche, CH)

This breakout session discussed the acceptability of RWD for regulatory/HTA decision making and provided recommendations on how to leverage its use:

- RWD can offer valuable information across the drug-development cycle, e.g. information on patient selection, clinical trial results interpretation, clinical effectiveness, pharmacovigilance, etc. The research questions, context of use, and analytical approaches should be defined clearly and prospectively (vs retrospective use to accommodate HA questions).
- RCTs are expected to remain the gold standard for regulatory approvals. However, alternative study designs including the use of external or hybrid control arms, or pragmatic studies generally seemed acceptable options in situations where conduct of RCTs is challenging, such as in rare cancers.
- There is a need to strengthen the case for the value of RWD in drug development and decision making and to establish best practices for RW study conduct.
- Categorization of evidence levels of RWE can help prioritize and plan studies according to the hierarchy of evidence (e.g. establishing the gold standard of RWE).
- Early and continuous engagement with relevant stakeholders on how to best leverage RWD to supplement regulator/HTA submissions is important, especially in challenging situations of very low patient numbers and no SOC.

Combined breakout sessions 2 and 4: patient voice and data-collection systems

Chairs: Roger Wilson (UK), Irmela Radtke (Roche, CH), Meghna Samant (Flatiron Health, US), and Bjørg Bolstad (Norwegian Medicines Agency, NO)

This session aimed to define a problem statement and brainstormed on possible solutions and recommendations:

- The overarching problem was defined as finding the best possible data set for registration and access in a fragmented world
- RWD is used for regulatory and HTA purposes, early R&D, research, clinical practice, and insurance companies. From an efficiency and systematic approach, there is need for an integrated RWD framework that applies to all these different worlds while also allowing a modular approach.

- Fragmentation at all levels (i.e. countries, healthcare systems, data sources, patient populations), was highlighted as a major issue suggesting that harmonization is a critical success factor.
- Harmonization of data-collection approaches (e.g. common data models) and need to identify **global solutions** beyond the EU or country level. Inclusion of such recommendations within ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) guidelines was mentioned as a possible option.
- Standards of data quality and strategies to handle missing data and ensure data consistency and completeness are needed, including consensus on endpoint definitions and assessment, linkage to genomic data, and capturing of comorbidities.
- The varied definitions of endpoints that exist can challenge the understanding of information.
- Integrating the patient voice into this discussion is critical. Patient involvement in the study design should be ensured to identify relevant outcomes; better information provision is required to support patients in coping with the disease.
- One of the fundamental challenges is heterogeneity of data coming from various sources. Cultural differences and privacy issues across Europe present another set of challenges.
- It was recommended to make optimal use of existing registries to ensure the best utilization of existing frameworks both at national and international level. How can the existing data be leveraged? A good example was given at the country level in Belgium where there is an inventory of all the different data sources in the country.
- There is ethical consideration of data privacy, data ownership, and patient consent. A new concept of informed consent may be required and future Cancer Drug Development Forum (CDDF) discussions can help address those issues.

Breakout session 3: ensuring robust decision making from the analysis of RWD

Chairs: Chris Harbron (Roche, UK) and Eva Skovlund (Norwegian University of Science and Technology, NO)

This section focused on the methodological aspects of generating robust RWD:

- While RCTs remain the gold standard, RWE can play an important role as a source of robust supplementary evidence for HA/HTA decision making. In addition, RWE can help optimize treatment by identifying the best approaches to sequencing and combinations.
- There is a need for global guidelines on data collection and analysis, including (a minimum set of) sensitivity analyses and adjustment for confounders.
- It is recommended to clearly specify study objectives and establish a rigorous statistical analysis plan aimed at testing and for adjusting for bias prior to study initiation, and for mitigation of missing data and false positive results.
- RWE studies should be planned prospectively (e.g. pragmatic clinical trials, observational studies), especially if conditional approval is the goal.
- Use of contemporaneous control (vs historical) is preferred in RCTs for rare cancers where external control is the only option.
- It was recommended to engage in ongoing dialogue with regulators and payers on RWD exercise requirements.
- Scientific advice should be sought to support qualification procedures for novel methodologies in order to harmonize approaches in the EU.

KEY TAKEAWAYS

John Smyth (CDDF Board, UK)

In a concluding note, Prof. John Smyth emphasized several key points made at the meeting and made a call for action:

- The importance of prospective RWD collection using the appropriate methodology to minimize biases was highlighted, in addition to the role of cancer registries in collecting robust RWD
- Identifying approaches to collaborate and leverage RWE across countries while complying with the General Data Protection Regulation (GDPR) and national



legislations will be critical and was identified as the focus of a future CDDF workshop.

- **Call for action**

- Define categories of RWD evidence level
- Apply a different approach for rare cancers versus common cancers
- Include harmonization efforts in RWD approaches
- Involve patients as key stakeholders

ABBREVIATIONS

CDDF, Cancer Drug Development Forum

CDK, cyclin-dependent kinase

COPD, chronic obstructive pulmonary disease

CRN, Cancer Registry of Norway

CRPC, castration-resistant prostate cancer

DRUP, Drug Rediscovery Protocol

EGFR, epidermal growth factor receptor

EHDEN, European Health Data and Evidence Network

EHR, electronic health record

EMA, European Medicines Agency

EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer core quality-of-life questionnaire

FDA, US Food and Drug Administration

GDPR, General Data Protection Regulation

HA, health assessment

HCP, healthcare professional

HER2, human epidermal growth factor receptor 2

HPV, human papilloma virus

HR, hormone receptor

HTA, health technology assessment

ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

INSPIRE, INcreaSe Pharmaceutical REporting

MCC, merkel cell carcinoma

MET, mesenchymal–epithelial transition

MTB, molecular tumour board

NGS, next-generation sequencing

NICE, National Institute for Health and Care Excellence

OMOP, Observational Medical Outcomes Partnership

OS, overall survival

PAH, pulmonary arterial hypertension

PFS, progression-free survival

PRO, patient-reported outcome

QALY, quality-adjusted life-year

QoL, quality of life

RCT, randomized controlled trial

RW, real world

RWD, real-world data

RWE, real-world evidence

SOC, standard of care



The Cancer Drug Development Forum would like to take a moment to thank all the speakers, programme committee members and session chairs who contributed greatly to our insightful discussions and the success of the meeting.

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Thank you for your interest in CDDF activities and continued support.