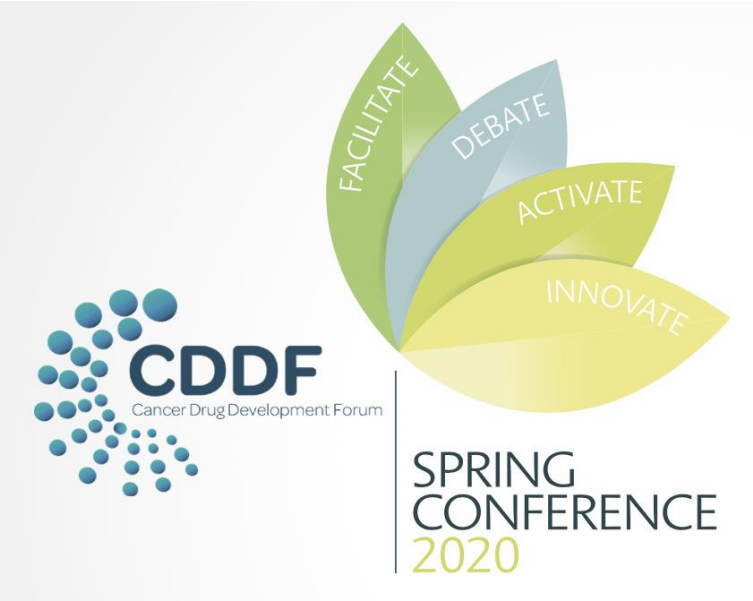

Workshop Summary:

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

Axel Glasmacher

CDDF Treasurer

Adjunct Professor, Faculty of Medicine, Univ. of Bonn (DE)

AG Life Science Consulting

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

CDDF Multi-Stakeholder Workshop

November 21–22, 2019

Amsterdam, Netherlands

PROGRAMME COMMITTEE

- John Smyth (University of Edinburgh - CDDF Board, UK) - Programme Chair
- Nafsika Kronidou Horst (Roche, CH)
- Stefan Schwoch (Lilly, UK)
- Eva Skovlund (Norwegian University of Science and Technology, NO)

CDDF 11TH SPRING CONFERENCE 2020
THE NETHERLANDS | 10-12 FEBRUARY 2020
WWW.CDDF.ORG

Many thanks to the Speakers, Session Chairs and Participants!

Speakers

- Valérie André
- Espen Enerly
- Chris Harbron
- Ralf Herold
- Cécile Ollivier
- Meghna Samant
- Elmar Schmidt
- Eva Skovlund
- Marlene Thomas
- Carin Uyl-de Groot
- Jaap Verweij
- Roger Wilson

CDDF MULTI-STAKEHOLDER WORKSHOP

USE OF REAL WORLD DATA TO OPTIMISE ONCOLOGY DRUG DEVELOPMENT AND ACCESS

6-7 July 2016
London, United Kingdom

European Journal of Cancer 101 (2018) 69–76

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ScienceDirect

journal homepage: www.ejcancer.com

Position Paper

The use of real-world data in cancer drug development

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[d] *University of Edinburgh, Edinburgh, UK*

Current “Real World” Data Landscape

- EMA + FDA definitions focus on routinely collected data
- Including old and new sources
  - Disease or product registries
  - Electronic health records, claims/insurance databases
  - Wearable technology, even social media
- Data quality is a major issue
  - FDA framework published
  - Several EU initiatives started (e.g. Good Registry Practice, EMA/HMA Big Data Task Force, RWD ecosystem common data model)

Regulatory Perspectives on Real World Evidence

- Evolution of regulatory science with **innovative clinical evidence generation and analysis** (incl. Monte Carlo methods, probalistic statistical inference)
- Steps towards accepted RWE approaches include **early discussions**, pre-agreed plans, methodology qualification processes and more.
- **Transparency, replicability of methods and reproducibility of results** are necessary to accept RWE

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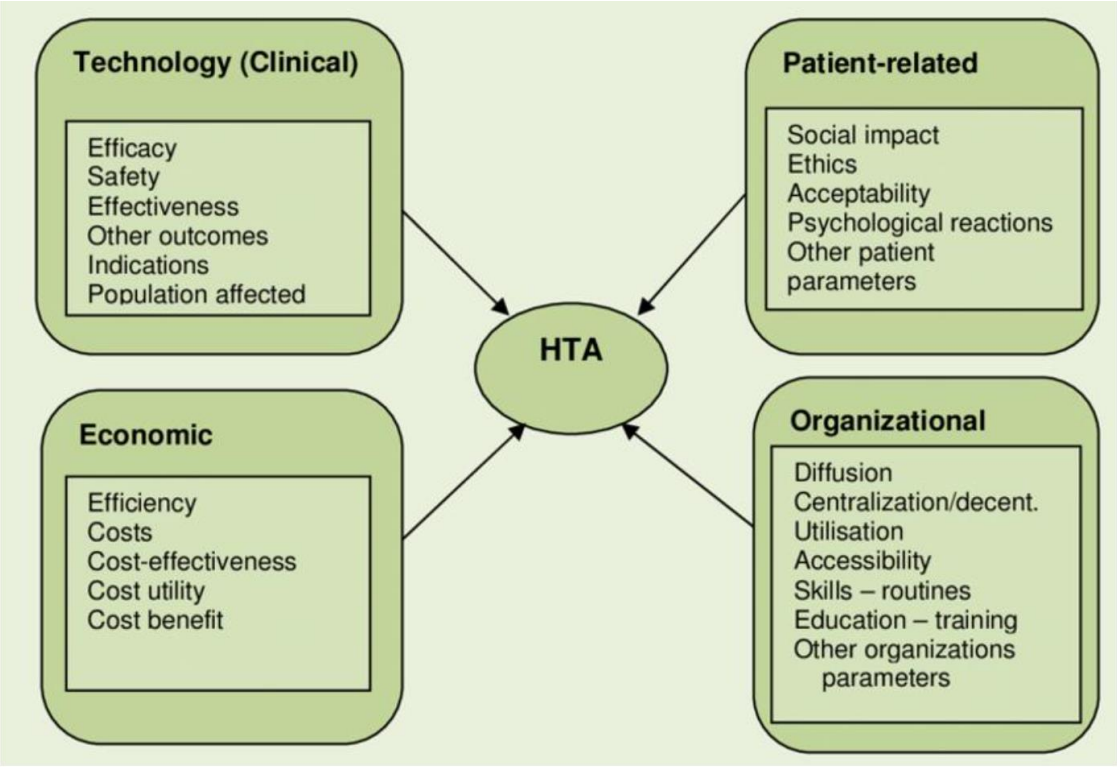
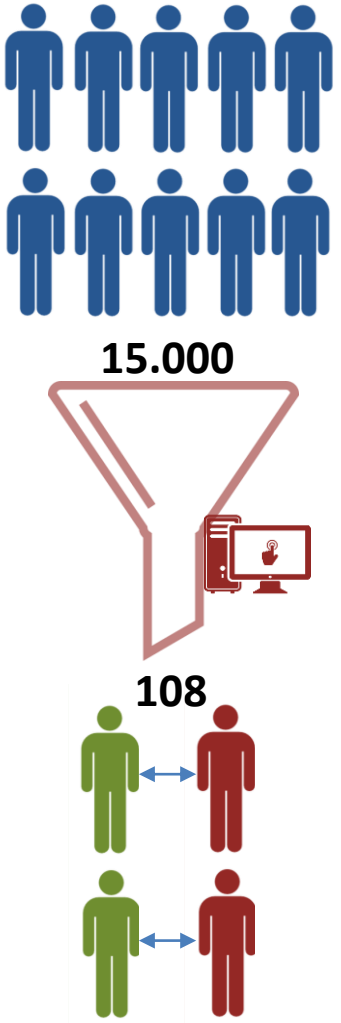
Health Technology Assessment



- Concern about unrepresentative patient populations in clinical trials (younger, less comorbidity)
- Use of RWE to understand multiple therapy lines and allow disease modelling
- Use RWD to design more representative RCTs

Case Study: Sharing Valuable Experiences

- External control for a single-arm, phase 2 study of a CDK 4/6 inhibitor in patients with HR+/HER- metastatic breast cancer
  - Source: Flatiron Health database cohort (total N=15.000)
  - Mahalanobis distance matching to select 108 controls
  - Key methodological challenges were
    - **Selection bias**
    - Lack of **contemporaneous controls** and
    - **Unintended 'cross-over'.**



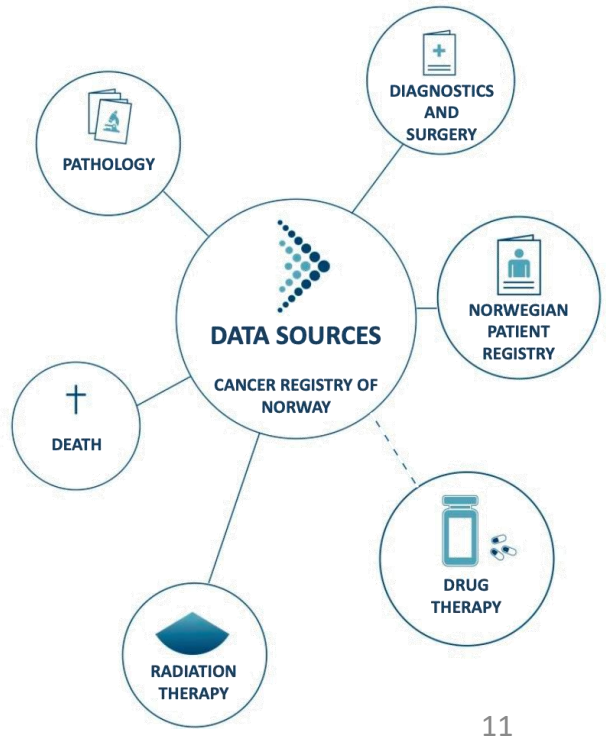
Personal Highlight

Potential Biases & Mitigations in Using External Controls

Potential Bias	Risk	Potential Mitigation
Selection bias	Different **patient populations** enrolled in clinical trial than in external control.	**Adjust for known confounding** due to differences in patient population
Calendar time bias	Patients treated in the **past** have **worse outcomes** than those treated **today** due to improvements in standard of care over time	Use data from **concurrently treated** external controls
Regional bias	Patient outcomes may **vary between regions** reflecting different healthcare practices between regions.	Use control patients from **same region**
Assessment bias	**Knowledge of therapy can influence** the outcome assessment.	Use a **robust, objective endpoint**
Different endpoint bias	Certain endpoints (e.g. ORR, progression) are **measured differently** in clinical trials than in routine clinical practice (e.g. using standards such as RECIST).	Use an endpoint that is **assessed in the same way** in the clinical trial as the external control
Immortal Bias	**Study start** for every patient **difficult to define** in external data. Differences compared to study can lead to bias.	Use data sources where we can **reliably define study start**, use the equivalent time zero.
Retrospective selection bias	**Retrospective selection** of external data and key analysis features.	**Prospective planning** and **transparent documentation** of all analyses
Study bias	Patients in clinical trials have **different outcomes than in clinical practice.**	An alternative source of external data may be another **clinical trial**

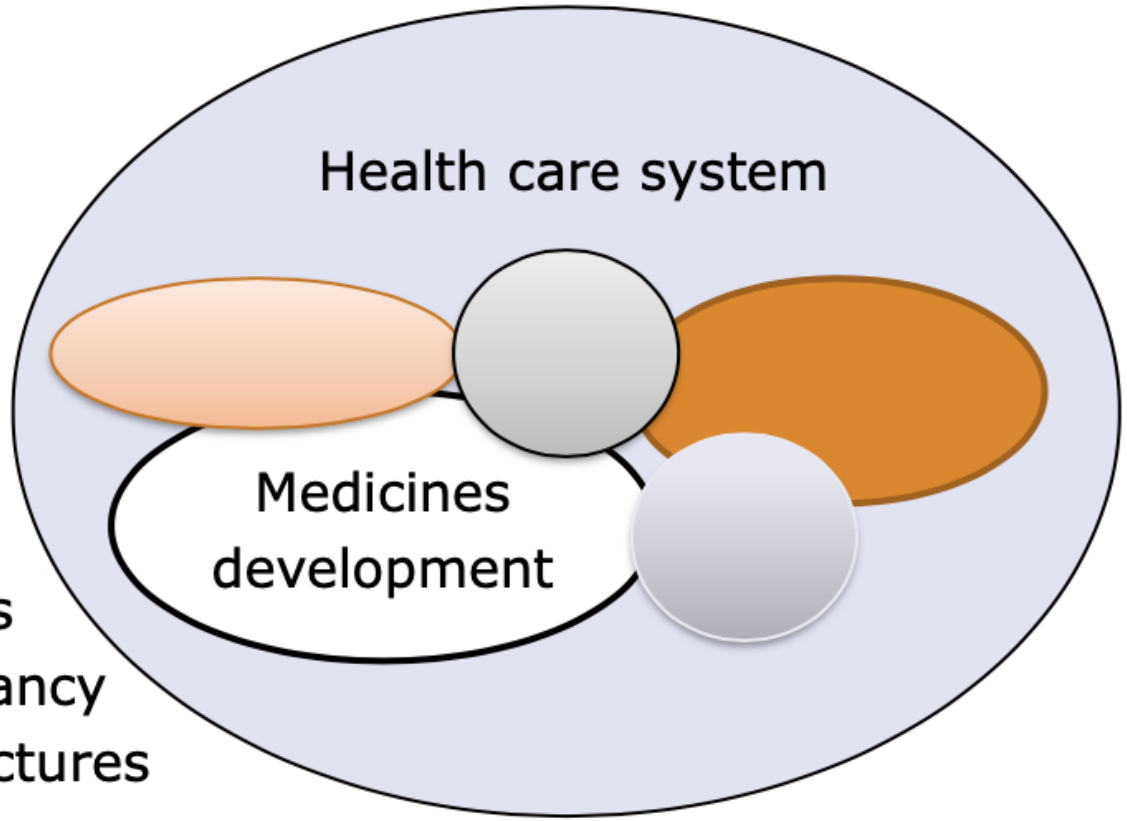
Disease-Based Registry. Norway

- Mandatory, exempt from patient consent
- Entries from multiple sources, tightly curated
- National statistics
  - All: Incidence, prevalence, survival
  - Partly: Diagnosis, therapy and follow-up
- Drug information added (work in progress
  - Collaboration with pharmaceutical companies and Norwegian Cancer Society
- Support of regulatory decisions, example:
  - Post-approval commitments for a HPV vaccine



Personal Highlight

Create a "Learning Health Care System"



Agents
Processes
Permancancy
Infrastructures

"science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience.
[… Such systems …] explicitly use technical and social approaches **to learn and improve with every patient who is treated.**"

5

http://www.learninghealthcareproject.org/section/background/learning-healthcare-system

Take Away Points (I): Global Needs

- ✓ **Regulatory/HTA frameworks** on the use of RWE for drug development. Guidelines on data collection and analysis.
- ✓ **Harmonization,** ideally led by European Commission or ICH. Establishment of best practices for RW study conduct.
- ✓ **Categorization of evidence** from RWE and **data quality standards** to ensure data consistency and completeness
- ✓ Efforts to overcome fragmentation of data and access to data through a **common data model**.
- ✓ A new concept of **informed consent** may be required

Share Best Practices

Take Away Points (II): Practical Recommendations

- ✓ Specify study objectives and **rigorous statistical analysis plan**
- ✓ **Plan RWE studies prospectively** and early
- ✓ Preferably use **contemporaneous control** (vs historic)
- ✓ Ensure early **patient involvement** in study design
- ✓ Engage in early and **ongoing dialogue with regulators and payer (incl. methodol. qualification procedures)**
- ✓ Make an **inventory of existing registries**

Thank you very much for your attention!

Quotes from regulators, HTA bodies, industry, clinicians, patients, and researchers expressed during the meeting

At the time of licensing, knowledge on true benefit–risk balance is frequently limited, as marketing authorization is often based on a single pivotal trial

RWD/RWE have the potential to transform the drug development process

Early discussion with relevant stakeholders and prospective planning of RWE studies for collection of the right data for the right purpose are important

New data sources without accepted analysis methods and clear purpose will not have a noticeable effect on regulatory decision-making. Seek scientific advice to support qualification procedures for novel methodologies

RWD open up opportunities for patient-centered research

There are limitations to RWD

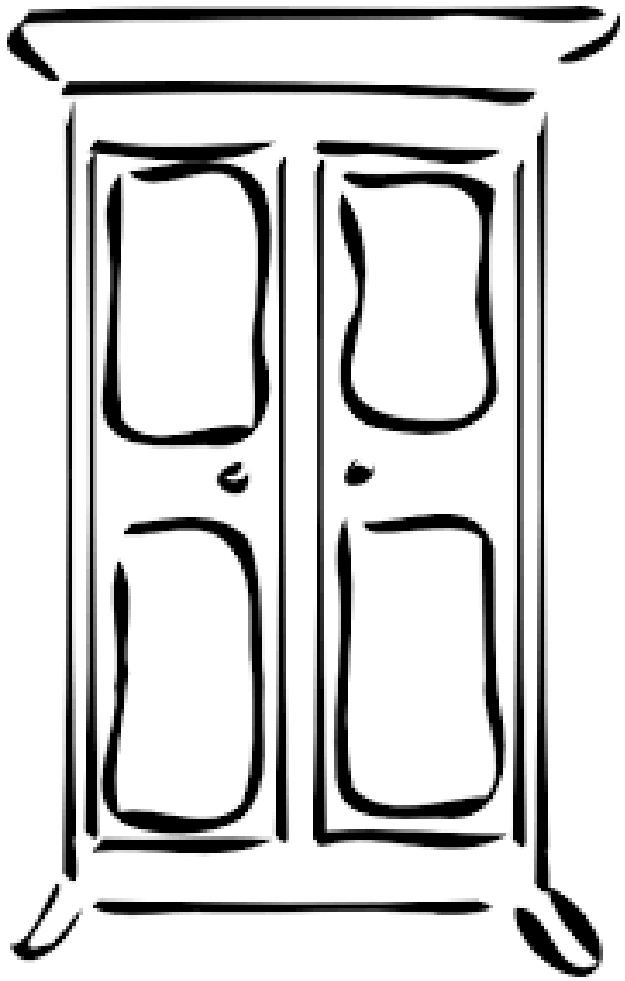
Cancer is increasingly becoming a rare disease

The empathy for building good RWD repositories is missing

EHR data have the potential to provide research-/regulatory-grade evidence and supplement evidence from clinical trials

From an HTA perspective, cost containment is crucial. Each new treatment product is associated with opportunity cost

BACKUP



Patient Demographics

Symptom relief & efficacy data

(country specific)

Patient Diary

Quality of Life (QoL)

Assessment

Safety Data

Clinical

Demographics, EHR Data, Lab Test Results, Diagnoses, Procedures, Pathology/ Histology Data, Radiology Images, Microbiology Data, Provider Notes, Admission/ Discharge and Progress Reports, Performance Status

Medication

Medication Orders, Administration (Dose, Route, NDC/RxNorm codes), Concomitant Therapies, Point of Sale Data, (Prescription & OTC) Prescription Refill, Allergies

Claims

Medical Claims, Prescription Drug Claims, Other Drug and Treatment Use Data

Molecular Profiling

Genomic and Genetic Testing Data (SNPs/Panels), Multi-Omics Data (Proteomics, Transcriptomics , Metabonomics, Lipidomics), Other Biomarker Status

Family History

Historical Data on Health Conditions and Allergies Relating to Patient and Extended Family, Smoking Status, Alcohol Use

Mobile Health

Fitness Trackers, Wearable Devices, Other Health Apps Measuring Activity and Body Function

Environmental

Climate Factors, Pollutants, Infections, Lifestyle Factors (diets, stress), Other Environmental and Occupational Sources

Patient Reported

Patient Reported Outcomes, Surveys, Diaries (diets, habits), Personal Health Records, Adverse Event Reporting, Quality of Life Measures

Social Media

Patient Communities, Twitter, Facebook, Blogs

Literature

Disease Burden, Clinical Characteristics, Prevalence/Incidence, Rates of Treatment, Resource Use and Costs, Disease Control, Quality of Life Measures