CDDF
Cancer Drug Development Forum

CDDF Multi-Stakeholder Workshop

INNOVATIVE ONCOLOGY TRIAL DESIGNS

18-19 SEPTEMBER 2023, NL

EXECUTIVE SUMMARY

CANCER DRUG DEVELOPMENT FORUM (CDDF)

CDDF Multi-Stakeholder Workshop

Innovative Oncology Trial Designs

(18-19 September 2023, NL)

Cancer Drug Development Forum (CDDF) Multi-Stakeholder Workshops are **neutral, non-competitive meetings** that address **topical issues** and **recent innovations in oncology drug development** with the aim of **improving cancer treatment**. The workshops facilitate multi-stakeholder discussion and collaboration, bringing together leading voices from academia, the pharmaceutical industry, regulatory authorities, and patient advocacy groups.

The workshop on "**Innovative Oncology Trial Designs**" took place on 18-19 September in Amsterdam (NL) to discuss **how novel techniques can be best implemented in drug development-related trials**, considering insights from all relevant stakeholders. It covered a range of topics, from **novel (and surrogate) endpoints**, **patient-reported outcomes** and harnessing **real-world data**, to **novel statistical designs** and **methods**.

This interactive meeting generated fruitful, thought-provoking discussions and emphasized collaborative efforts among all stakeholders with the following key takeaways:

SESSION 1: ENDPOINTS FOR INNOVATIVE CLINICAL TRIALS

KEY TAKEAWAYS

- ·**RECIST** are validated, and **adaptable/evolvable**, e.g. iRECIST for immunotherapy. Current considerations are **ctDNA and radiometric assessments**, but **not yet been validated**.
- ·It takes **8-10 trials to validate a surrogate endpoint**; there are no novel validated surrogate endpoints at this time.
- ·**Distinct early- and late- endpoints** for conditional approvals may be considered – e.g. ORR.
- ·Ensure **maturity of data** - e.g. for PFS to imply OS.
- ·**Patient-meaningful endpoints** are considered at the **individual level** for quality and robustness; it is accepted that they may not be statistically powered.

NEXT STEPS

- ·Harmonise **HTA, regulatory**, and **patient needs**.
- ·**Artificial Intelligence** will likely revolutionise endpoints, but will require confirmation and validation.

SESSION 2: INNOVATIVE TRIAL DESIGNS AND ESTIMANDS

KEY TAKEAWAYS

- ·When **designing clinical trials**, it is essential to precisely **define the objective** of the trial, **formulate the research question** in a clear way and **consider the population** as well as the research context when selecting the most appropriate study design. Study design, outcomes collected and analysis methods need to be predefined and **allow answering of the research question formulated**.

- ·**Good planning** from the start and writing the protocol in a clear way that provides **clear arguments** for the selected design is essential both for **standard and innovative design**. This also applies to the good reporting of clinical trials.

- ·**Adaptive trial methodology** can be used to increase the **efficiency of clinical trial designs** and has been applied successfully in the **early-phase** setting.

- ·**Innovation of methodology** should not be for its own sake, its added value should be in **facilitating the answering** of the research question.

- ·**The estimands framework** is an essential framework for all future studies, to ensure the design starts by focusing on the research question and **frames the five components (population, endpoints, summary measure, treatment conditions,** and **handling of intercurrent events)** clearly. This subsequently guides data collection and statistical analysis.

- ·**The estimands framework** should be used for scientific advice and other interactions with regulators. It **requires a cross-functional approach** and **input from other experts** beyond statisticians.

- ·**The estimands framework** affects all aspects of clinical trial design, conduct and analysis and s**hould become the norm in future conversations on clinical trials.** We need all experts to adopt it.

SESSION 2: INNOVATIVE TRIAL DESIGNS AND ESTIMANDS

NEXT STEPS

- ·Ensure **any conversation on clinical trial innovation starts** with asking "**What is the scientific question?**"; define the estimand and select the methods to fit the question and the context.

- ·Share **more examples and learnings** from the use of **adaptive trial designs** as well as the **use of the estimands framework** to increase awareness and adoption.

- ·**Encourage and enable cross-stakeholder** and cross-functional **collaboration on estimands,** especially in non-statistical fora.

- ·Provide **training to iDMCs and ethics committees** to understand innovative trial designs and the estimands framework.

SESSION 3: TOWARDS PATIENT-CENTRIC EVIDENCE GENERATION

KEY TAKEAWAYS

- ·**Patient Preference Data (PPD)** can impact a wide range of decisions, from clinical development to regulatory approval, access/reimbursement and individualized treatment decision-making: it is not just about clinical efficacy!

- ·Stakeholders should work together to **define, incorporate and collect PPD** without duplicating efforts. Patient involvement is essential (e.g. design and analysis).

- ·External Control ARM (ECA) trials are **alternatives to a trial internal control arm** and can be **considered when RCTs** are **unethical, unfeasible or lack equipoise** (e.g rare indications / molecular subgroups, significant unmet medical need, limited treatment options, paediatric indications).

- ·They are **not a shortcut** and definitely not a low-burden effort: they require a convincing rationale that an RCT is not feasible, large high-quality quality and complete databases, a strong design and analytical plan, and they are less able to detect small/moderate differences. Draft FDA guidance is in place.

- ·High burden to demonstrate that the ECA meets the bar for valid treatment comparison.

- ·Pragmatic trials are meant to **inform decision-makers**, **enhance generalizability** by enrolling a population relevant to the decision in practice, and **streamline data collection** or measure a broader range of outcomes.

- ·Extensive, **multidisciplinary/multistakeholder discussions**, including **regulatory guidance**, are key to their design (feasibility and clinical context), conduct (operational and logistic aspects) and ultimate success.

SESSION 3: TOWARDS PATIENT-CENTRIC EVIDENCE GENERATION

NEXT STEPS

- ·Data and endpoints (PPD) that are meaningful to patients should be at the centre of every clinical trial, so **appropriate and regular collection of PPD should be an integral part of trial design**, as per other endpoints (OS, PFS, RR). The original clinical trial is the best time to collect and make good use of PPD.

- ·ECA trials represent a resource, particularly in certain domains, however **hybrid randomized** designs (e.g. phase II single arm and registrational phase III with hybrid control arm[SS1] [GR(2]) may provide more robust results to support drug approval and reimbursement.

- ·Pragmatic trials are instrumental in increasing **generalizability**, granting appropriate **flexibilities** and offering **access to trials** to a higher number of patients willing to participate. Constant dialogue with regulators and HTA bodies is key.

SESSION 4: PRACTICALITIES ON INNOVATIVE CLINICAL TRIALS

KEY TAKEAWAYS

- Rational combination therapies aim to maximise efficacy and overcome resistance. But there are important **practical mechanistic and regulatory considerations** for trial design (contribution of components), and its preclinical package (activity, interaction), that can differ between the FDA and EMA. **Cellular therapies may open new challenges**.

- For **rare cancers** (and rare subtypes), we need to **identify and engage with the population**, minimise heterogeneity, and **work in collaborative networks**. Regulators understand that size constraints inevitably limit Phase 3 endpoints. Surrogate end-points can be important and higher uncertainty must be expected while maximising the robustness of the data and external validation. www.rarecancerseurope.org has established consensus recommendations.

- **Platform studies improve the efficiency of trials** with shared design, documentation, reference appendices, populations, selection, costs/contracting, data, biomarkers and even control arms. **However, practicalities and planning ahead are essential for central deliverability,** site manageability and patient accessibility. **Simplicity**, where possible, **is key**. Master protocols effectively run multiple trials through one document and need to align their data delivery/cleaning/analysis, and handle evolving arms and populations.

- **Updates to ICH E6 (GCP) and E8** (General Considerations for Clinical Studies) **are designed to improve the design**, conduct and value of clinical trials. Ethics, scientific approach and patient involvement are the general underlying principles. **Stakeholder** (participant and investigator) **involvement**, in a quality continuum, using a proportionate and efficient risk-based approach, aims to better focus efforts on ensuring that **results support useful decision-making**.

SESSION 4: PRACTICALITIES ON INNOVATIVE CLINICAL TRIALS

NEXT STEPS

- **Combination and platform studies** would benefit from guidance such was developed for rare cancer studies.
- Please read ICH E8 (R1) and E6 (R3) together and please respond to the ICH E6 (R3) GCP consultations by 30th September. Note ICH E6 Annex 1, with Annex 2 drafting underway.
- Explore **how to address the accessibility of patient information sheets** and the consent process within Europe.
- Explore **how to support training of ethics committees** and IDMCs.

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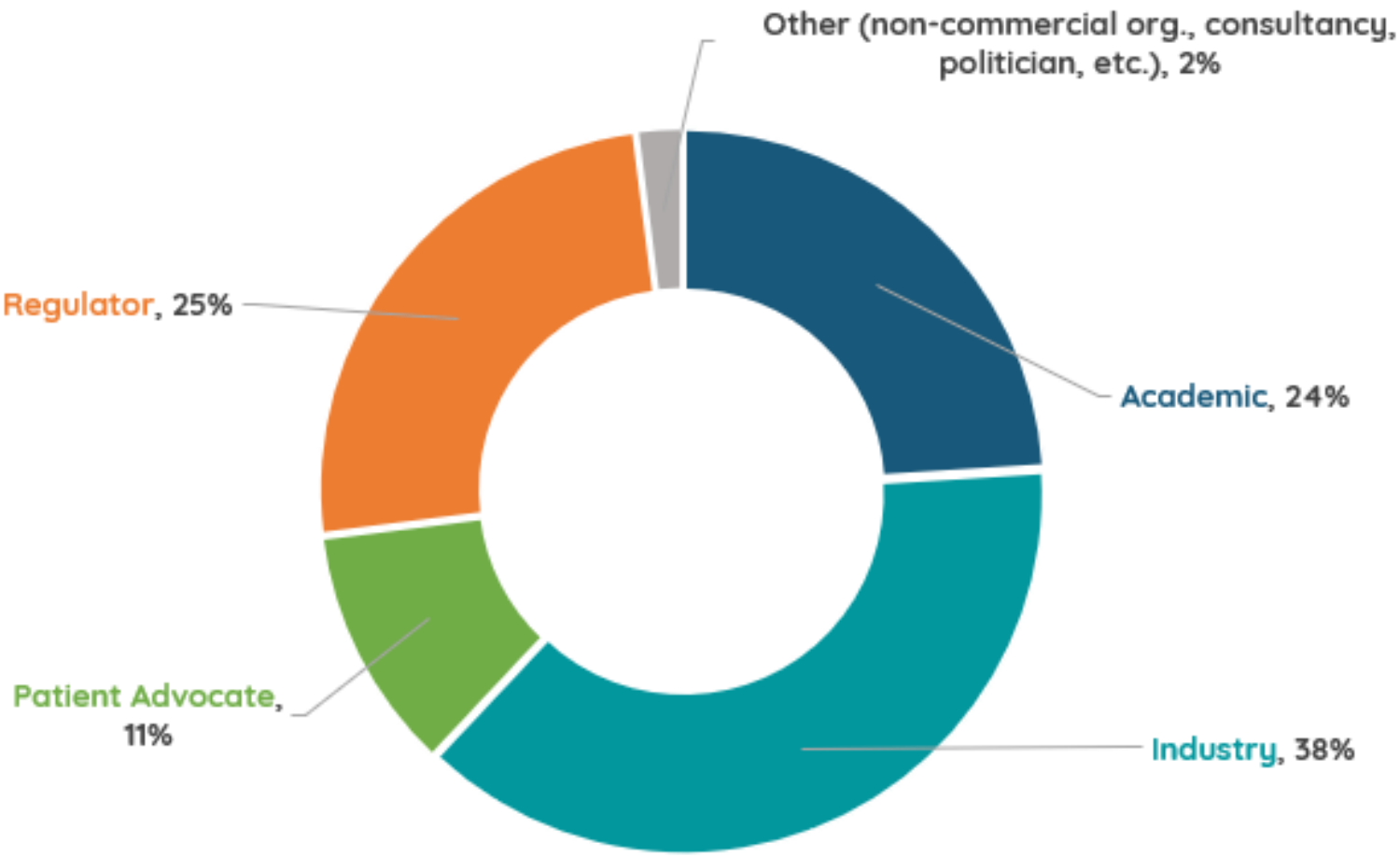
Cancer Drug Development Forum

Collaboration and open dialogue among **all stakeholders** are **key** to accelerating and improving oncology drug development for patients

AUDIENCE AT THE CDDF WORKSHOP

The CDDF's meetings present **a wide range of prespectives** from **various stakeholders** who are involved in the development of oncology drugs. Our **multi-stakeholder, collaborative approach** facilitates a productive dialogue in a neutral, non-competitive space in order to **accelerate effective cancer drug development.**

Onsite Participants & Speakers



169
ONLINE ATTENDEES

59
IN-PERSON ATTENDEES

WHAT PARTICIPANTS SAY ABOUT CDDF'S DISCUSSION?

"From the discussion, it became rather clear that in essence all stakeholders struggle with the relevance and interpretability of surrogate endpoints. Opinions differ whether they are sufficient for everyone or what criteria should be applied to declare them validated.
The highlights were the recognition that regulators and HTAs are struggling with the same problems, but that in general each of the stakeholders is trying to make the best out of the situation within the framework of their mandate."

Anja Schiel
Norwegian Medicines Agency, NO

"Session 1 was a lot about endpoints and I really thought that that was an interesting and patient centric topic to discuss. Because endpoints really do need to be patient friendly. Having an endpoint that is not relevant to the patient experience is not going to be a successful trial by any strategy."

Rachel Giles
International Kidney Cancer Coalition, NL

"As a cancer of unknown primary and broader rare cancer patient advocate, the key lesson for me is that there are still too many trials poorly, small, and mono-nationally designed. I am also excited by the time spent on the topic of External Control Arm trials, as with the potential of delivering more personalized oncology to patients, study populations will become more targeted and potentially smaller hence this will be even more important in the future."

Warnyta Minnaard
Missie Tumor Onbekend, NL

"What I like the most about the workshop is the discussion we have amongst each other. Agreements, disagreements and exchange of ideas. What we can pick up from that. Also the so-called corridor talk where people talk about all topics that keep them busy. That's where we learn the most."

Jan Bogaerts
EORTC, BE

"My favorite thing about the workshop is the ability to listen to great topics, interact, and have discussions during coffee breaks and during meals. We are talking about really important things happening right now in drug development for cancer patients and we have all stakeholders in the room."

Beatrice Lavery
Roche, CH

The views expressed in this page are the personal views of the participants and may not be understood as being made on behalf of or reflecting the position of the regulatory agency/agencies or organisations with which the participants are employed/affiliated.

JOIN THE CDDF'S **OPEN DISCUSSIONS** & ENGAGE WITH **MULTI-STAKEHOLDER COMMUNITY**

WEBINAR DETAILS

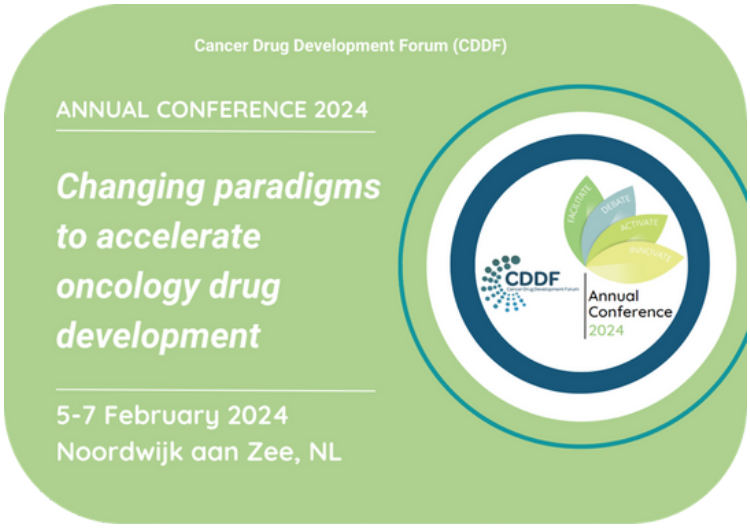
- **Date & Time**
  Thursday 28 September 2023
  16:00 (CEST) / 10:00 (EDT)
- **Speakers**
  Marcus Guardian (EUnetHTA, NL)
  Julie Spony (European Patients' Forum, FR)

Webinar outline | Registration

Session Topics

1. **Setting the Scene of Biomarkers**
2. **Companion Diagnostics, Approval & Reimbursement**
3. **Towards Patient-Centric Evidence Generation**
4. **Practicalities on Innovative Clinical Trials**
5. **Workshop Wrap-up and Next Steps**

Program | Registration



Session Topics

1. **Real-World Evidence**
2. **Reflections on CDDF Meetings in 2023**
3. **Decentralized Care and Trials**
4. **Impact of Recent Regulatory Changes**
5. **Drug & Biomarker Combination**

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