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WE WILL BE STARTING AT 1PM ET

10.18.2022

What have we learned: Adapting to regulatory guidance and experience

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Agenda

RWE: Shifting perspectives and recent regulatory guidance

Jillian Motyl Rockland, MPH

Director, Real World Evidence
Flatiron Health

Leveraging a clinico-genomic database for companion diagnostics (CDx) post approval studies

Brian Clancy

Director, Real World Data Solutions
Foundation Medicine

Contextualizing single arm trial data with RWE

Evgeny Degtyarev

Director, Biostatistics
Novartis

Panel Discussion & Live Q&A

Brian Clancy

Evgeny Degtyarev

Lynn Howie

Jillian Motyl Rockland (Moderator)

Which of these applications of RWD has your organization historically either considered or incorporated in regulatory submissions?

A. Characterizing natural history or unmet medical need

B. As an external comparator to a single arm trial

C. Satisfying post-marketing requirements or commitments

D. To expand a label into new indications

E. For global market access including HTA

F. None of the above

RWE: Shifting perspectives and recent regulatory guidance

Jillian Motyl Rockland

Director, Real World Evidence
Flatiron Health

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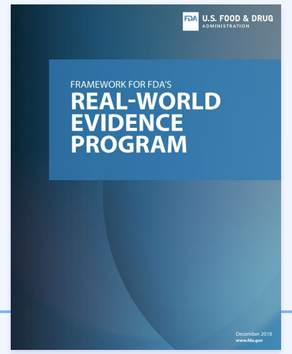
Health authorities' perspectives on the regulatory use of RWE is continuously evolving as evidenced by the release of RWE guidances over time



2018

FDA RWE Framework

2019

FDA Guidances

2020 – 2021

EMA 2025 Vision: RWE

2021 – 2022

FDA Guidances: 2021/22

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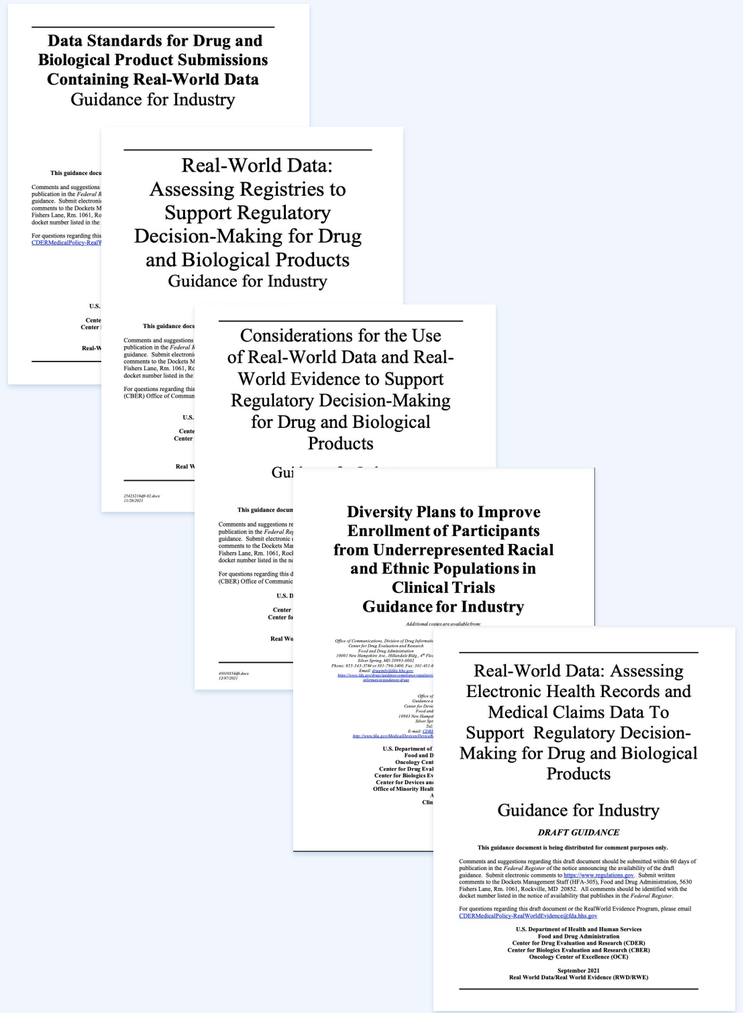

2021 – 2022

Probability of RWE regulatory success varies depending upon the use case

RWE contribution to the totality of evidence:

Evidence to **inform trial design**

Supportive evidence contributes but does not standalone

Substantial evidence adequate and well-controlled to form the basis of a decision about safety and/or efficacy

Increasing bar for regulatory acceptance

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Key considerations when using RWD for regulatory applications:

Start with why

Engage early and often

Be transparent

FDA has signaled specific circumstances in which RWD can support traditional evidence

- **Significant unmet need,** limited available therapies
- **Rare cohorts** of interest, making randomized trials infeasible
- Expected **large effect size** from preliminary data (e.g., from clinical trials)
- **Existing body of evidence** around safety / efficacy of a drug in related population(s)

"In limited instances, FDA has accepted RWE to support drug product approvals… often when using a parallel assignment control arm is ***unethical or not feasible and usually when the effect size is expected to be large****, based on preliminary data."*

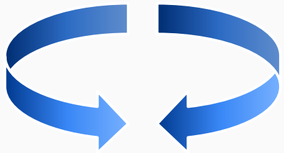
—

FDA's framework for RWE program

- Duke Margolis Whitepaper: Determining Real-World Data's Fitness for Use and the Role of Reliability
- Framework for FDA's Real-world evidence program

Advanced planning and ongoing communication are critical

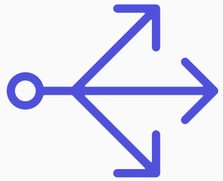
Proactively plan to use RWE to fill gaps in evidence package	Collaboratively develop study design and SAP	Discuss proposed study design and SAP prior to analyses
Sponsor	**Sponsor**	**Sponsor**
RWD provider	**RWD provider**	**RWD provider**
Health Authorities	Health Authorities	**Health Authorities**



Interactions are iterative and ongoing throughout the RWD study design and execution

Be clear on what RWD **is** and **is not**

Patient level data is available



Describe data processing and transformations

Be open about limitations

Potential for confounding or bias

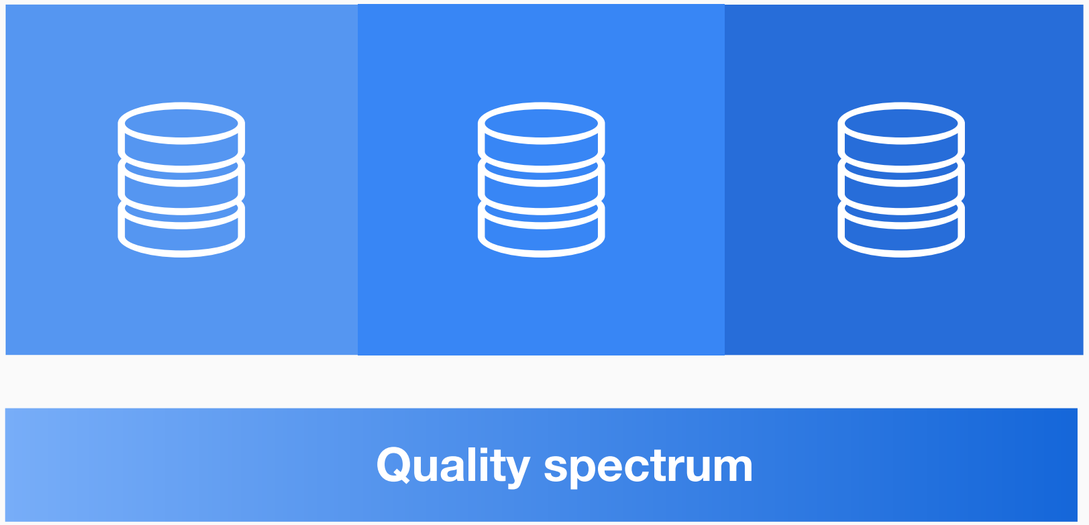
Data is fit for purpose and missingness is addressed

Perception

Data quality is **binary**

Reality

Data is **fit for purpose**



Continuously learning and adapting

Health Authority perspectives on use of RWE to support regulatory decision making are **continuing to evolve**

The bar for successful regulatory use of RWE **increases as it plays a larger role** in the evidence package

Upfront **planning & communication** are key for maximizing likelihood of regulatory success.

Transparency is critical

Leveraging a clinico-genomic database for companion diagnostics (CDx) post approval studies

The Approval of the ROS1 CDx

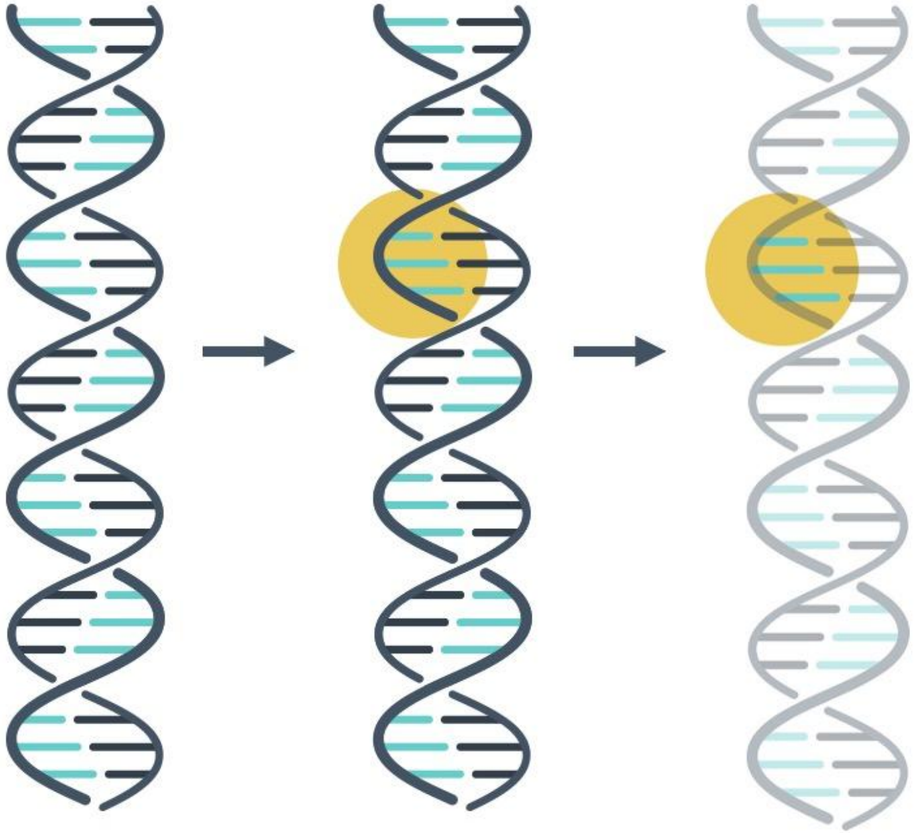
Brian Clancy, Director, RWD Solutions, Foundation Medicine

October 2022

FOUNDATION MEDICINE

Uncovering Deep Genomic Insight

Foundation Medicine utilizes Next Generation Sequencing (NGS) to **provide patients, oncologists and researchers with high-quality genomic insights.**



FOUNDATION MEDICINE

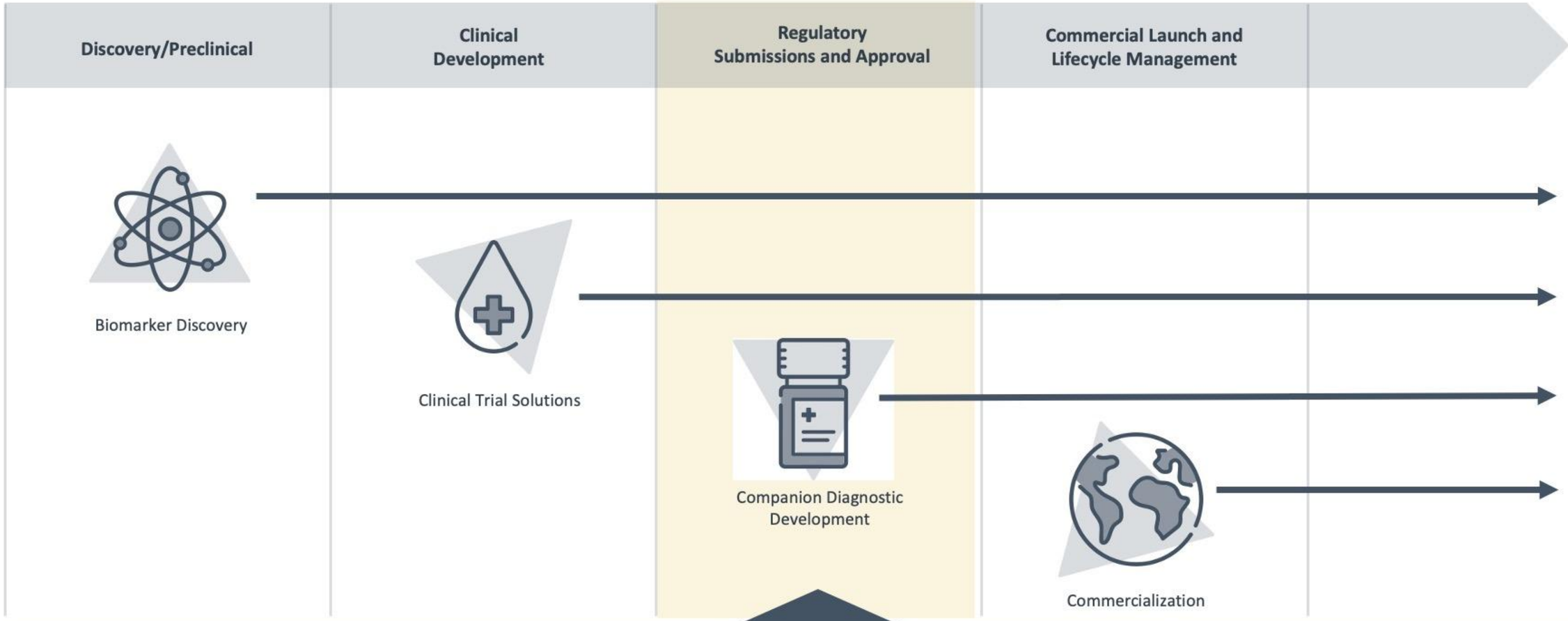
Empowering Informed Treatment Decisions

The Foundation Medicine Report

- Foundation Medicine test reports provide genomic findings and relevant therapeutic options based on these findings inclusive of any FDA-approved companion diagnostic (CDx) indications

FOUNDATION MEDICINE

Enabling Drug Discovery, Development and Commercialization



New drugs targeting biomarker-specific populations generally require a CDx to gain and/or maintain approval by the FDA

FOUNDATION MEDICINE

Entrectinib CDx Approval

- On June 9, 2022, the U.S. Food and Drug Administration (FDA) approved FoundationOne®CDx to be used as a companion diagnostic for the two current indications for Rozlytrek (entrectinib).
  - This means physicians will be able to use FoundationOne CDx to identify patients with NTRK gene fusions across all solid tumors or non-small cell lung cancer (NCSLC) patients with ROS1 fusions who may benefit from treatment with Rozlytrek (entrectinib)
- When ROS1 gene fusions occur, generally in 1-2 percent of NSCLC diagnoses,[1] cancer cells grow and proliferate in an uncontrolled manner.

1. American Cancer Society. Targeted Drug Therapy for Non-Small Cell Lung Cancer. Available from: https://www.cancer.org/cancer/lung-cancer/treating-non-small-cell/targeted-therapies.html

FOUNDATION MEDICINE

Leveraging CGDB for CDx Post Approval Study (1/2)

- Limited clinical research data exists on ROS1-mutated NSCLC because the condition is rare. Although Foundation Medicine conducted a traditional clinical validation study for FoundationOne®CDx using clinical bridging, the study was limited by a small number of available clinical trial specimens.
- A series of interactions with FDA led to a conversation about how clinico-genomic RWD could be used to generate additional evidence to further assess the clinical effectiveness of FoundationOne®CDx.
- As a condition of this approval, Foundation Medicine intends to conduct a post-approval study powered by the Flatiron Health – Foundation Medicine Clinico-Genomic Database (CGDB).[1] The study will examine relevant clinical endpoints to further demonstrate FoundationOne®CDx's ability to identify patients with ROS1- mutated NSCLC who may respond to Rozlytrek (entrectinib).

1. U.S. FDA Approves FoundationOne®CDx as a Companion Diagnostic for Rozlytrek® (entrectinib) from: https://www.foundationmedicine.com/press-releases/3fe223c4-f8ae-4c35-b138-47ad284f6452

FOUNDATION MEDICINE

Leveraging CGDB for CDx Post Approval Study (2/2)

- The CGDB offers attributes consistent with relevant regulatory guidance and, with demonstrated success in supporting regulatory submissions, CGDB is a compelling option for regulatory use cases
  - As an example, Foundation Medicine in collaboration with Flatiron Health has the capability to perform analytical pipeline reruns on historical Foundation Medicine sample data to ensure a consistent match between current CDx biomarker definitions and cohort selection in CGDB. This is of critical importance for retrospective studies of a novel CDx.
- We see this as an important step forward in using real-world data to complement the regulatory approval process and look forward to ongoing partnership with Genentech and Flatiron Health as we implement this innovative approach to post-approval evidence generation.

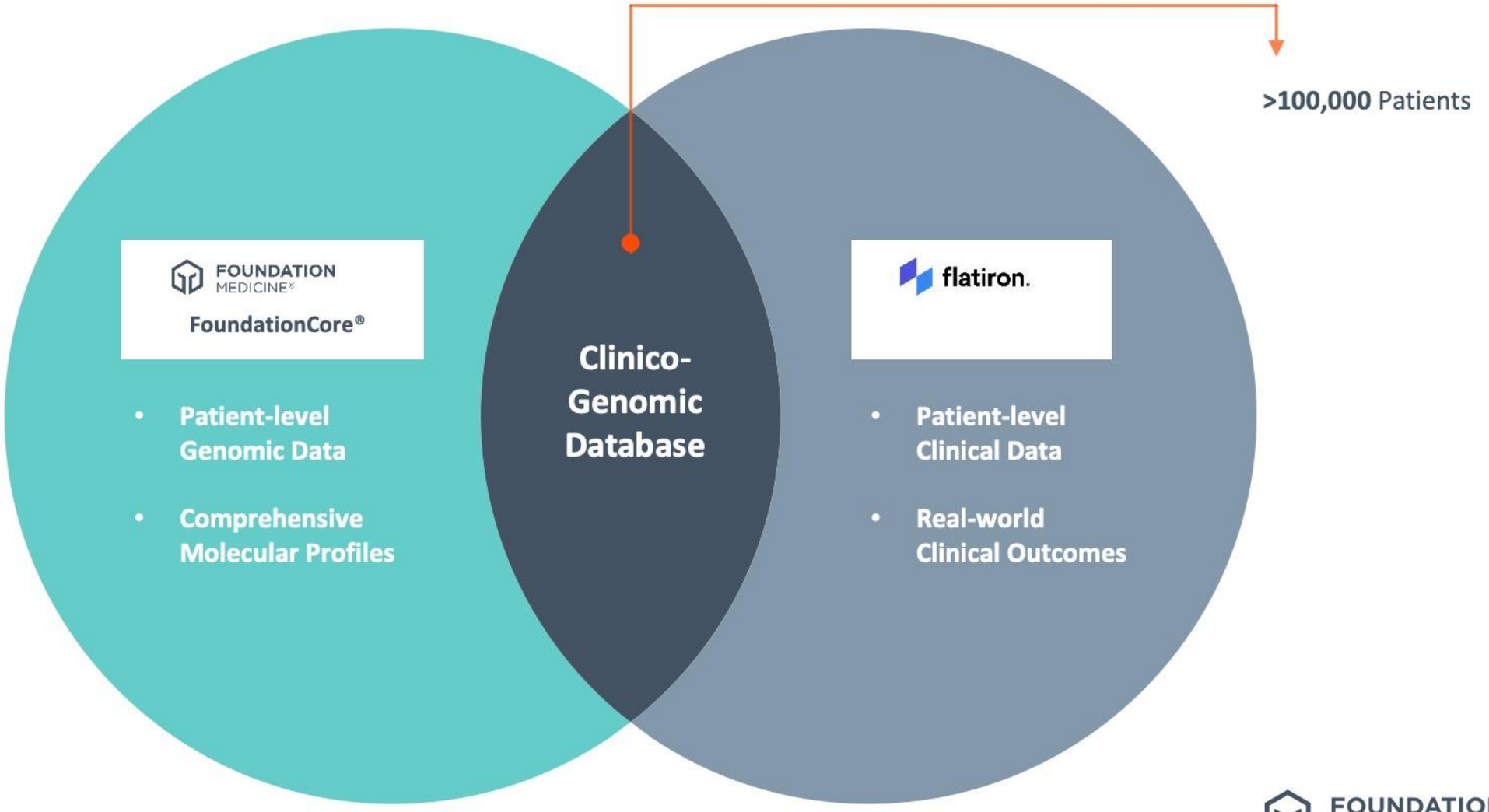
FOUNDATION MEDICINE

Perspectives

1. Precision Oncology inevitably results in rare patient populations
2. For Companion Diagnostics for rare conditions that depend on tissue availability for clinical bridging studies, it seems likely that there will be increasing need to supplement clinical trial data with real-world data to enhance evidence that a CDx identifies patients who may respond to therapy
3. The ROS1 CDx approval is an example of where the availability of high-quality clinico-genomic real-world data may enhance the probability of regulatory success for a CDx

FOUNDATION MEDICINE

A Transformative Clinico-Genomic Database



FOUNDATION MEDICINE

Contextualizing single arm trial data with RWE

Evgeny Degtyarev, Director Biostatistics, Novartis

ResearchX webinar

October 18, 2022

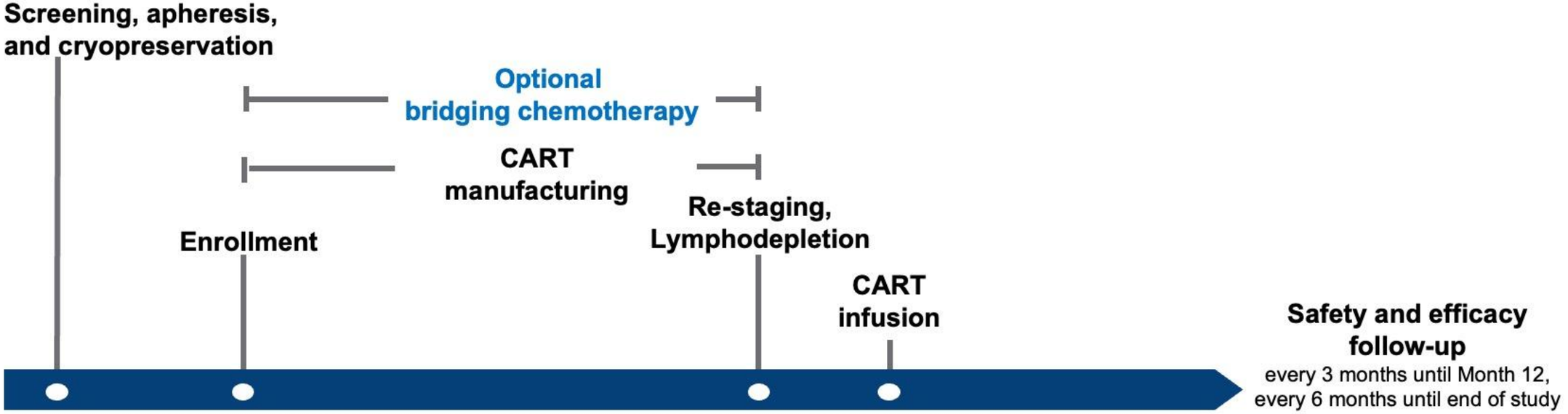
NOVARTIS | Reimagining Medicine

Oncology drug development

- Randomized clinical trials (RCT) gold standard for providing evidence for regulatory approval of new medicines
- Single-arm trials (SAT) considered for regulatory approval when randomized trials are infeasible or unethical to conduct
  - Rare diseases
  - Unmet need in last line of therapy with no effective standard of care
  - Highly promising early data impacting ethics/integrity of RCT
- Substantial number of approvals in oncology primarily supported by SAT
  - 22 approvals by EMA between 2010-2019*
  - 25% of approvals in oncology by FDA between 2008-2016**

* Tenhunen et al. (2020) Clin. Pharmacol. Ther., 108: 653-660
** Zhou et al. (2019) J Natl Cancer Inst. 2019 May 1;111(5):449-458

ELARA: single arm trial with tisagenlecleucel in 3L+ follicular lymphoma



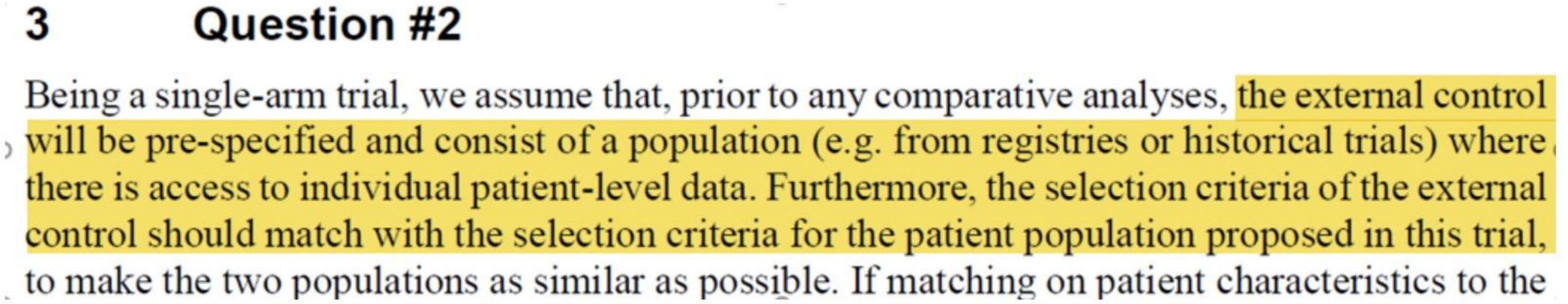
- Tisagenlecleucel is an anti-CD19 chimeric antigen receptor T cell (CAR-T) therapy approved in multiple countries for the treatment of pediatric pts up to and including 25 years of age with relapsed / refractory (r/r) B-cell ALL*, adult pts with r/r DLBLC* and adult patients with r/r follicular lymphoma* (FL)
- CAR-T therapies are personalized cell therapies requiring manufacturing after enrollment

*Please refer to locally approved label for detailed indication information; trial results published in Fowler et al. (2022)

NOVARTIS | Reimagining Medicine

External control group relevant for HAs

- Need for external control with **patient-level data** highlighted by the Norwegian Health Authorities (Tisagenlecleucel rapporteur country) during protocol review:



3 Question #2

Being a single-arm trial, we assume that, prior to any comparative analyses, the external control will be pre-specified and consist of a population (e.g. from registries or historical trials) where there is access to individual patient-level data. Furthermore, the selection criteria of the external control should match with the selection criteria for the patient population proposed in this trial, to make the two populations as similar as possible. If matching on patient characteristics to the

Two sources of real-world data used to contextualize ELARA data with RWE

ReCORD-FL

- a non-interventional retrospective cohort study based on chart review
- Data collection in academic centers in EU and North America by an electronic data collection form (eDCF) via a secure web-based data collection portal

Flatiron

- a non-interventional study utilizing electronic health records from the US Flatiron Health Research Database (FHRD)

Totality of the data expected to support a comprehensive efficacy assessment of tisagenlecleucel in r/r FL patients

CHMP Scientific Advice

Key questions

- Adequacy of the ELARA study to support filing considering the results from indirect comparisons with patient-level external data sources (from ReCORD and FHRD) are provided
- Adequacy of the external data sources
  - criteria for cohort selection
  - data collection and data quality
  - suitability of real-world endpoints
- Analysis methodology aiming to contextualize the ELARA results
  - Use of target trial and estimand frameworks* to emulate randomized trial, to define the question of interest and the corresponding analysis to address this question

* Hernan, Robins (2016); Hampson et al. (2021)

CHMP Scientific Advice

Key feedback

- "Contextualization of the single arm trial by indirect comparisons useful understand the efficacy of tisagenlecleucel in the current therapeutic landscape"
- RWE is supportive and compelling results from pivotal trial is key to a successful approval
- Agreement that the data sources could provide appropriate external control
  - "The credibility of the comparison will mainly depend on the sample size, the completeness of the data, the comparability of the study populations, the ability to adjust for important covariates, and the alignment of outcome definitions."
  - Data collection period for RWE restricted to coincide with the introduction of the currently used efficacy criteria as well as the last relevant EMA approval
- Use of target trial framework and proposed methodology endorsed
  - Additional sensitivity analyses included

Applying target trial framework
Clarity in interactions with all stakeholders

Component	Target randomized clinical trial (to be emulated)	Description of the emulated trial using SAT and RW cohorts	
		SAT	RW cohort
Eligibility	Inclusion/exclusion criteria of SAT study	Same as target trial	Inclusion/exclusion criteria of SAT study that are feasible to implement in retrospective assessment in the RW cohort
Treatment	Optional bridging therapy followed by lymphodepleting therapy and CAR-T infusion vs SOC	Same as target trial	
Treatment assignment	Block randomized, stratifying by key prognostic factors	CART after optional bridging therapy and LD therapy	One eligible line of therapy (index line) per patient will be selected based on the highest propensity score to be in SAT study.
Endpoint	CR per Lugano criteria	CR per Lugano criteria	CR based on real world response
Follow-up for endpoint	Randomization date	Enrollment date	Prescription date not available in RW cohort: we assumed SOC treatment start is very close to assignment
Causal effect	Effect of prescribing CAR-T vs SOC is assessed in patients who participated in SAT study		
Summary measure	Difference in CRR after prescribing CAR-T vs SOC	Difference in CRR after enrollment in SAT study vs after being treated with SOC	

SAT: Single arm study, RW: Real-world, LD: Lymphodepleting

Outcome of EMA submission and current status

- Tisagenlecleucel approved in relapsed/refractory follicular lymphoma*
  - RWE data not accepted for inclusion in the EU label
- EPAR: “These *(RWE)* studies are despite the remaining uncertainty of the effect estimates nevertheless **providing valuable context, and are in general deemed supportive of the pivotal study**, due to the clear differences in outcomes they show.”
- Remaining uncertainty:
  - not possible to fully emulate the inclusion criteria in the E2202 study
  - some prognostic values missing
  - differences in response criteria
- HTA submissions using RWE ongoing

EPAR: European Public Assessment report, HTA: Health Technology Assessment
*Please refer to locally approved label for detailed indication information

Conclusions

- RWE relevant for regulators and payers
  - more clarity about the role of RWE for drug labels needed
- Cross-functional collaboration within the company required incl. clinical, statistical, real-world evidence, regulatory, market access experts
  - significant time commitment considering limited experience - early planning and regulatory consultations critical
- Target trial and estimand frameworks facilitate transparent and structured discussion about RWD sources
- Further dialogue between sponsors, regulators, payers and academia needed to develop best practices and guidances, e.g. for sensitivity analyses and to clarify the role of RWE for drug labels

References

- Fowler, N.H., Dickinson, M., Dreyling, M. et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. Nat Med 28, 325–332 (2022).
- G. Salles, S.J. Schuster, L. Fischer et al. A Retrospective Cohort Study of Treatment Outcomes of Adult Patients With Relapsed or Refractory Follicular Lymphoma (ReCORD-FL). Hemasphere. 2022 Jun 21;6(7):e745. doi: 10.1097/HS9.0000000000000745. PMID: 35813099; PMCID: PMC9263496.
- Y. Hao, W-C Hsu, C. Parzynski et al. Utilization of External Control Arm to Contextualize Clinical Efficacy of Tisagenlecleucel Treated Among Patients with Relapsed/Refractory Follicular Lymphoma from the Single-Arm Elara Trial, Blood, Volume 138, Supplement 1, 2021, Page 4506, ISSN 0006-4971, https://doi.org/10.1182/blood-2021-152685.
- Miguel A. Hernán, James M. Robins, Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available, American Journal of Epidemiology, Volume 183, Issue 8, 15 April 2016, Pages 758–764
- L.V. Hampson, E. Degtyarev, Rui Tang et al. (2021) Comment on “Biostatistical Considerations When Using RWD and RWE in Clinical Studies for Regulatory Purposes: A Landscape Assessment”, Statistics in Biopharmaceutical Research
- L. V. Hampson, J.Chu, A.Zia, J.Zhang, W-C Hsu, C.Parzynski, Y.Hao, E.Degtyarev Combining the target trial and estimand frameworks to define the causal estimand: an application using real-world data to contextualize a single-arm trial, https://arxiv.org/abs/2202.11968

Over the next 1-2 years, which regulatory applications of RWD do you think your organization will pursue?

A. Characterizing natural history or unmet medical need

B. As an external comparator to a single arm trial

C. Satisfying post-marketing requirements or commitments

D. To expand a label into new indications

E. For global market access including HTA

F. None of the above

Panel Discussion

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Flatiron Health

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Q&A

Please submit questions through the Q&A feature at the bottom of your screen.

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