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Improving healthcare decisions

Advances in the Development of Real-World Evidence: Lessons from the US and China

ISPOR 2022 Annual International Conference
National Harbor, Maryland, USA

May 15–18, 2022

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Presentation topics



- **Introduction and Overview**
  Moderator: Eric Q. Wu, Ph.D., Analysis Group, Inc., Boston, MA, USA



- **Part I – Introduction to an Effective Methodology for Patient-Centric RWD Generation**
  Min Yang, M.D., Ph.D., Analysis Group, Inc., Boston, MA, USA



- **Part II – Empowering Real-World Research in China: Challenges and Solutions**
  Jia Zhong, Sc.D., Analysis Group, Inc., Boston, MA, USA



- **Part III – Practical Experience in Utilizing Real-World and Clinical Trial Data for Assessing Treatment Effects**
  L.J. Wei, Ph.D., Harvard T.H. Chan School of Public Health, Boston, MA, USA

- **Q & A**

Real-world evidence (RWE)

- The generation of RWE is increasingly playing an essential role in health care decision making. There are strong demands for high quality RWE from regulators, payers, and practitioners
- However, broader use of RWE has been limited by challenges in data quality
- New approaches for data collection and statistical methodologies have been developed to cope with such challenges

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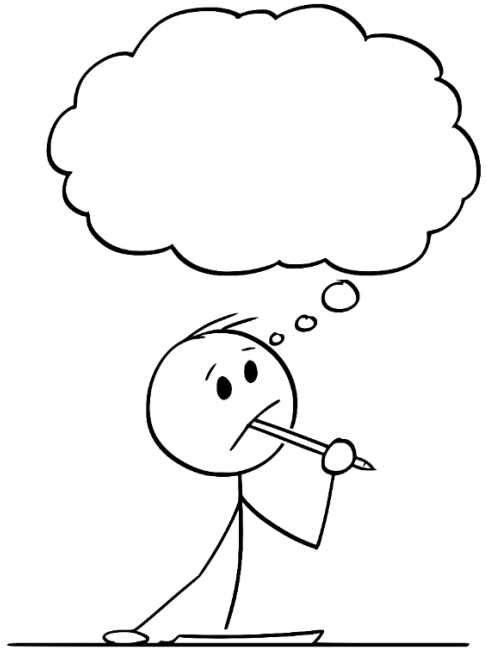
Part I – Introduction to an Effective Methodology for Patient-Centric Real-World Data (RWD) Generation

Min Yang, M.D., Ph.D.
Vice President, Health Care, Analysis Group, Inc.

What will be covered

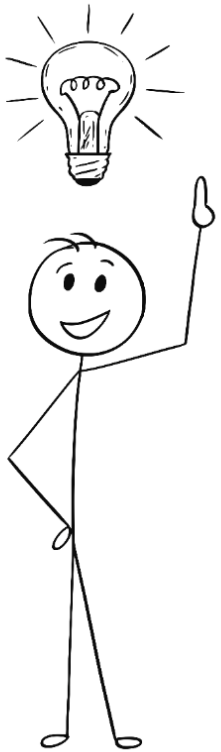
- Patient-centric RWD opportunities and challenges
- An introduction to the LEAP methodology
- What does LEAP offer in terms of patient-centric RWD generation?
- An example of the LEAP application
- Summary and recommendations

Patient-centric RWD opportunities and challenges



- While clinical trials remain the gold standard for product approval, their limitations are also well recognized
- At the time of product approval, stakeholders (regulators, payers, clinicians, patients) require/desire early patient-centric evidence from the real world
- Conventional RWD (e.g., health insurance claims, electronic health records and related chart reviews, or registries) usually takes time to mature and is often not adequate to generate high-quality patient-centric (e.g. QoL, symptoms) evidence
- Challenges:
  - Can we generate patient-centric RWD early after the launch of innovative products?
  - Can we capture baseline data at treatment initiation in order to assess benefits?
  - Can we ensure sufficient longitudinal follow-up with a good retention rate?

An introduction to the LEAP methodology

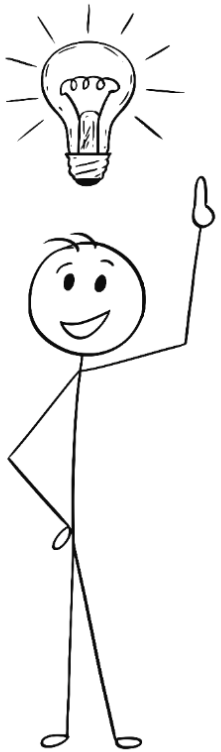


LEAP – Longitudinal Surveys of Patients with Recruitment through Patient Support Programs

- L – Longitudinal
- E – Survey
- A – Patients
- P – Programs

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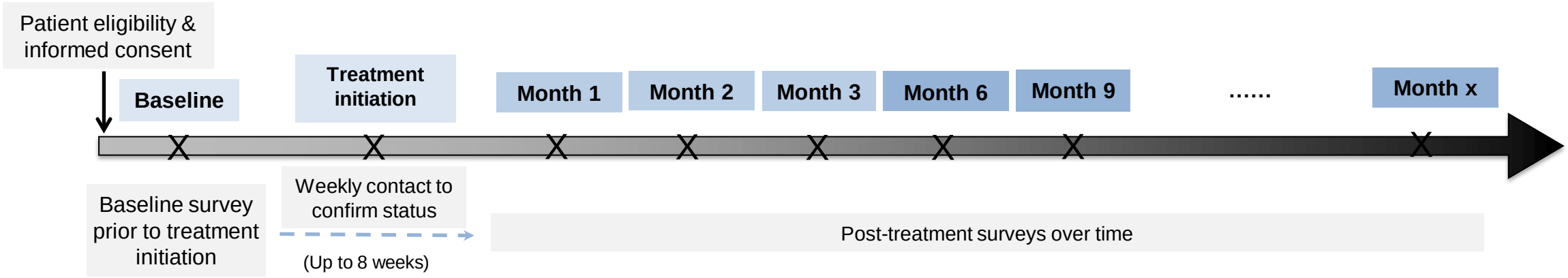
What does LEAP offer in terms of patient-centric RWD generation?



- Reflective of patient profiles in clinical practice
- Reflective of key characteristics in signs/symptoms and impacts on patients
- Geographic/practice representation (e.g., not limited to centers of excellence)
- Capturing true baseline (i.e., patient status at the time of treatment initiation)
- Timely RWE for an early view of patient experiences before vs. after treatment start
  - Inform post-product-launch value proposition
  - Inform treatment decisions
- Long-term follow-up to reflect sustainable treatment effect
- High retention rate

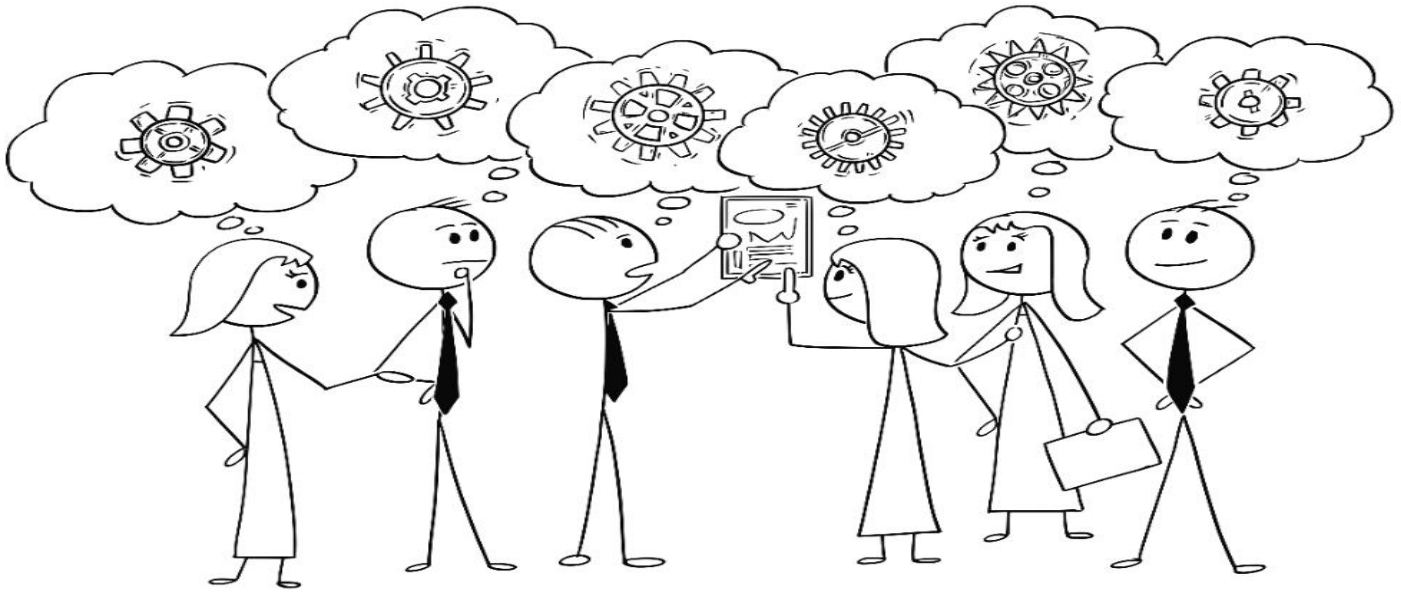
Introduction to the LEAP mechanism – operation

- In contemporary medicine, many biopharmaceutical companies offer patient support programs (PSPs) to help patients navigate the treatment journey
- PSPs offer an opportunity to recruit patients and follow them over time, allowing real-time evidence generation to support newly launched products



Introduction to the LEAP mechanism – alignment

- Critical to gain alignment and have a coherent coordination process across multiple involved parties (e.g., legal, compliance, adverse event reporting/pharmacovigilance, PSP vendor)



Example: the RELIEVE-AD project

JAMA Dermatology | Original Investigation

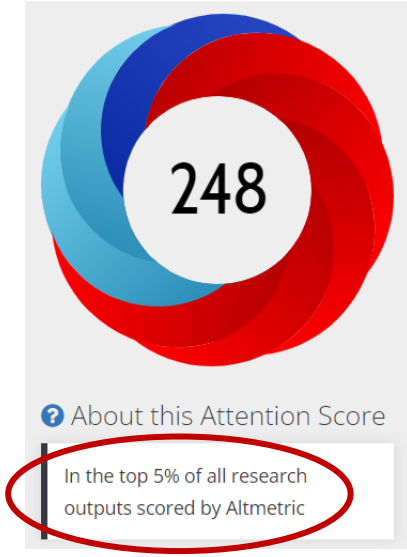
Treatment Outcomes Associated With Dupilumab Use in Patients With Atopic Dermatitis

1-Year Results From the RELIEVE-AD Study

Bruce Strober, MD, PhD; Usha G. Mallya, PhD; Min Yang, MD, PhD; Sohini Ganguli, PharmD; Abhijit Gadkari, PhD; Jessie Wang, ScD; Debra Sierka, PharmD; Dimittri Delevry, PharmD; Alexa B. Kimball, MD, MPH

ALL RESEARCH OUTPUTS	OUTPUTS FROM JAMA DERMATOLOGY	OUTPUTS OF SIMILAR AGE	OUTPUTS OF SIMILAR AGE FROM JAMA DERMATOLOGY
#100,686	#78	#3,838	#3
of 20,568,640 outputs	of 3,135 outputs	of 436,390 outputs	of 52 outputs

Altmetric has tracked 20,568,640 research outputs across all sources so far. Compared to these this one has done particularly well and is in the 99th percentile: it's **in the top 5% of all research outputs ever tracked** by Altmetric.



Altmetric – Treatment Outcomes Associated With Dupilumab Use in Patients With Atopic Dermatitis

What is the RELIEVE-AD project?

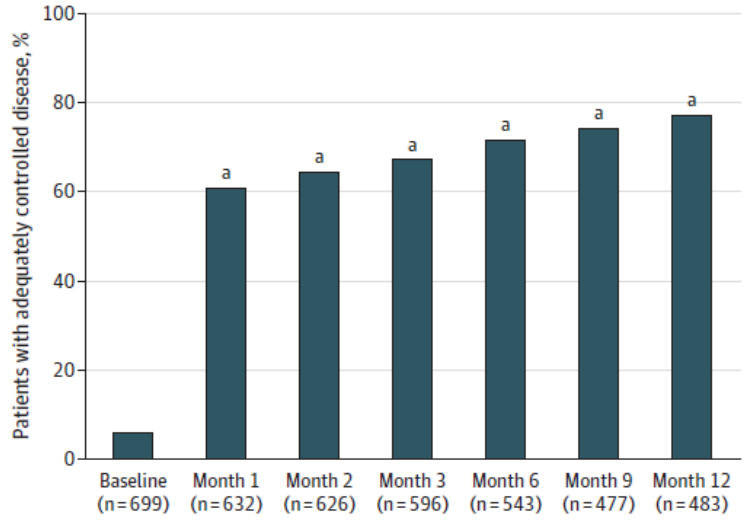
- Incepted in 2017, a pre-post, prospective, observational, longitudinal patient cohort study leveraging the PSP to recruit patients and follow them over time

- Core objectives: to describe experiences of patients with moderate to severe atopic dermatitis (AD) before and after initiating a new treatment

Selected Year 1 study findings

- Focused on signs, symptoms, disease-specific impacts, HRQL, treatment satisfaction, work productivity and activity

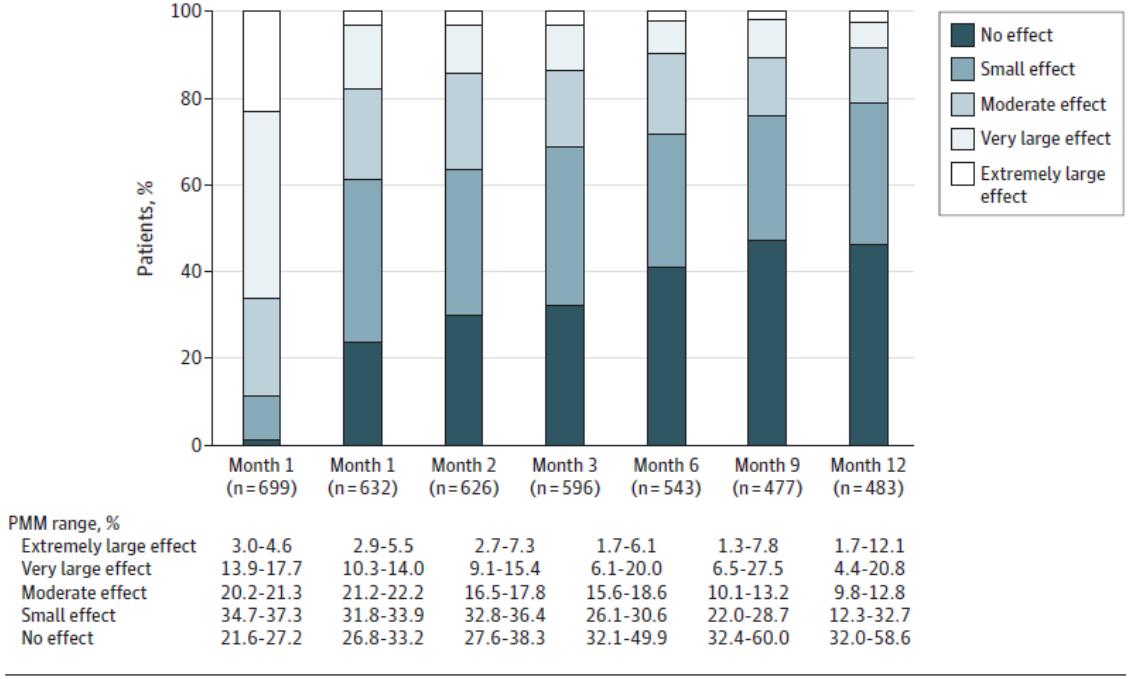
Figure 1. Disease Control Assessed Using the Patient-Reported Atopic Dermatitis Control Tool (ADCT)



Adequate disease control reflects a total ADCT score lower than 7.

[a] $P < .001$ vs baseline.

B Effect of atopic dermatitis on patients' lives based on DLQI



PMM range, %						
Extremely large effect	3.0-4.6	2.9-5.5	2.7-7.3	1.7-6.1	1.3-7.8	1.7-12.1
Very large effect	13.9-17.7	10.3-14.0	9.1-15.4	6.1-20.0	6.5-27.5	4.4-20.8
Moderate effect	20.2-21.3	21.2-22.2	16.5-17.8	15.6-18.6	10.1-13.2	9.8-12.8
Small effect	34.7-37.3	31.8-33.9	32.8-36.4	26.1-30.6	22.0-28.7	12.3-32.7
No effect	21.6-27.2	26.8-33.2	27.6-38.3	32.1-49.9	32.4-60.0	32.0-58.6

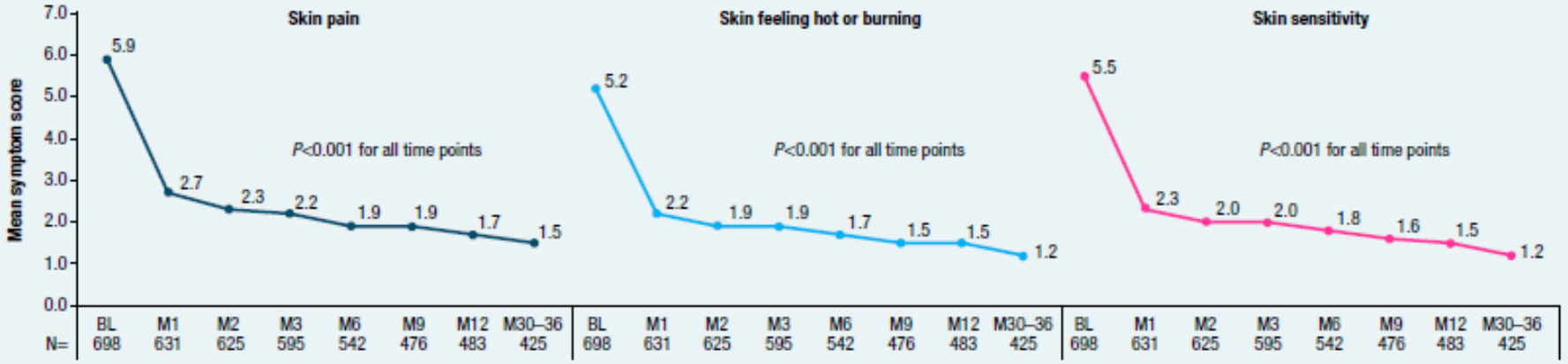
A, Percentage of patients with clinically meaningful change (≥4 points) on the DLQI.[30] B, Effect of atopic dermatitis on patients' lives based on DLQI (bands of 0-1 = no effect, 2-5 = small effect, 6-10 = moderate effect, 11-20 = very large effect, and 21-30 = extremely large effect).[29]

Strober B, Mallya UG, Yang M, Ganguli S, Gadkari A, Wang J, Sierka D, Delevry D, Kimball AB. Treatment Outcomes Associated with Dupilumab in Patients with Atopic Dermatitis: 1-Year Results From the RELIEVE-AD Study. JAMA Dermatology 2022;158:142-150

Selected Year 3 study findings – symptoms

Substantial and significant symptom improvements observed at Month 1 and sustained through 3 years

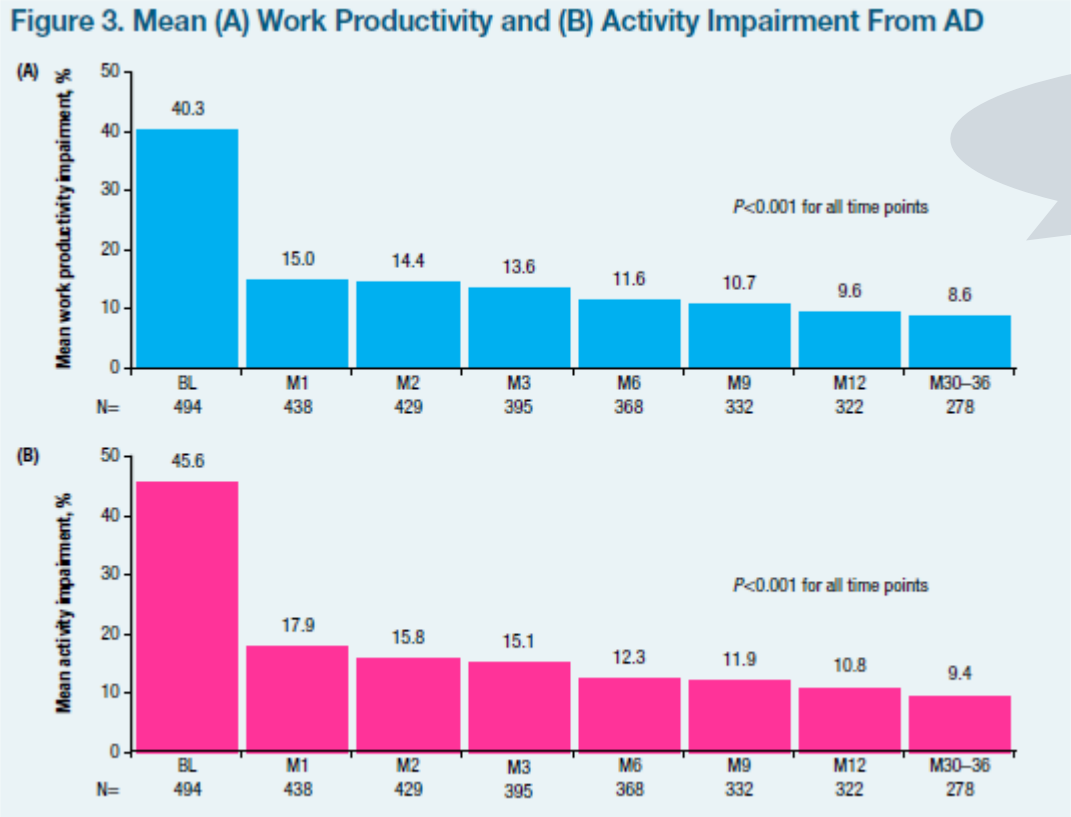
Figure 3. Symptom Scores for AD-Related Skin Pain, Burning, and Sensitivity



AD=atopic dermatitis; BL=baseline; M=month
Symptom score range for each category was 0–10; a score of 0 indicates no symptoms. Each category asked the patient to recall the average level over the previous week. All post-treatment initiation time points and imputed ranges were significantly improved from BL ($P<0.001$).

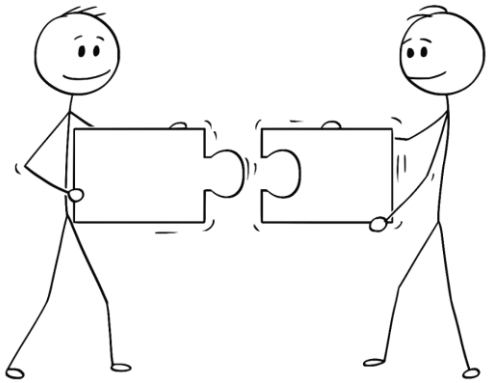
Strober B, Chao J, Chuang C, Yang M, Shumel B, Wang J, Bego-Le-Bagousse G, Sierka D, Wang Z, Delevry D. "Dupilumab Improves Patient-Reported Outcomes Among Adults With Moderate-to-Severe Atopic Dermatitis (AD) in Clinical Practice: 30-36 Month Results From the RELIEVE-AD Study" at the American Academy of Dermatology (AAD) Annual Meeting, March 25–29, 2022, Boston, MA

Selected Year 3 study findings – productivity, activity



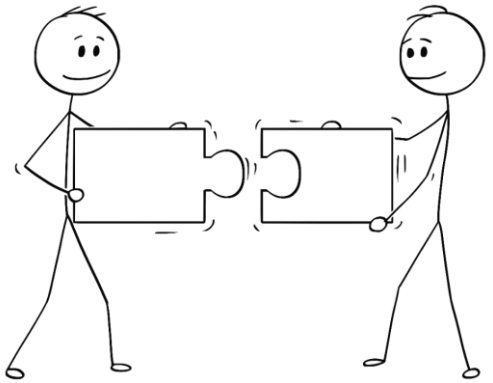
Substantial and significant productivity and activity improvements observed at Month 1 and sustained through 3 years

Delevry D, Chao J, Chuang C, Yang M, Shumel B, Martins B, Bego-Le-Bagousse G, Sierka D, Wang Z, Strober B. "Long-Term Dupilumab Effectiveness on Health-Related Quality of Life (HRQoL) and Work Productivity in Atopic Dermatitis (AD): Results From the RELIEVE-AD Study" at the American Academy of Dermatology (AAD) Annual Meeting, March 25–29, 2022, Boston, MA



Summary and recommendations

- Such studies are highly valuable for diseases that are symptomatic and substantially impair patients' HRQL, productivity, and daily life over time
  - Have been applied in dermatology, respiratory conditions, gastroenterology, neurology, etc.
- Data on real-time patient-reported outcomes fulfill the evidence gap for patient experiences directly from a patient's perspective following the launch of a new product
  - Timely data access
  - Informative for payers, regulators, and clinicians
- When setting up appropriately, a high retention rate over time provides the possibility for an in-depth assessment of the real-world long-term effectiveness



Summary and recommendations (cont'd)

- Data collection relies on self-reporting
  - For patients who are not capable of self-reporting (e.g., pediatric patients, patients with mental illnesses or very severe diseases), caregivers could take on the role as the proxy responders
  - Where appropriate, this can be also a venue to capture impacts on caregivers (burden for taking care of the patient and improvements derivative of patient outcomes)

- Be mindful of data interpretation and generalizability (e.g., selection bias, recall bias, attrition, missing data, etc.)

- With careful planning, this methodology provides another effective solution for patient-centric RWE generation

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Part II – Empowering Real-World Research in China: Challenges and Solutions

Jia Zhong, ScD
Manager, Health Care, Analysis Group, Inc.

Agenda

- Opportunities and challenges in China's real-world research
- Examples highlighting real-world data (RWD) solutions in China
  - Example 1: Innovative solutions for common RWD challenges – an oncology example
  - Example 2: A nimble alterative to generate early and reliable evidence under logistic constraints
- General recommendations for generating real-world evidence (RWE) in China

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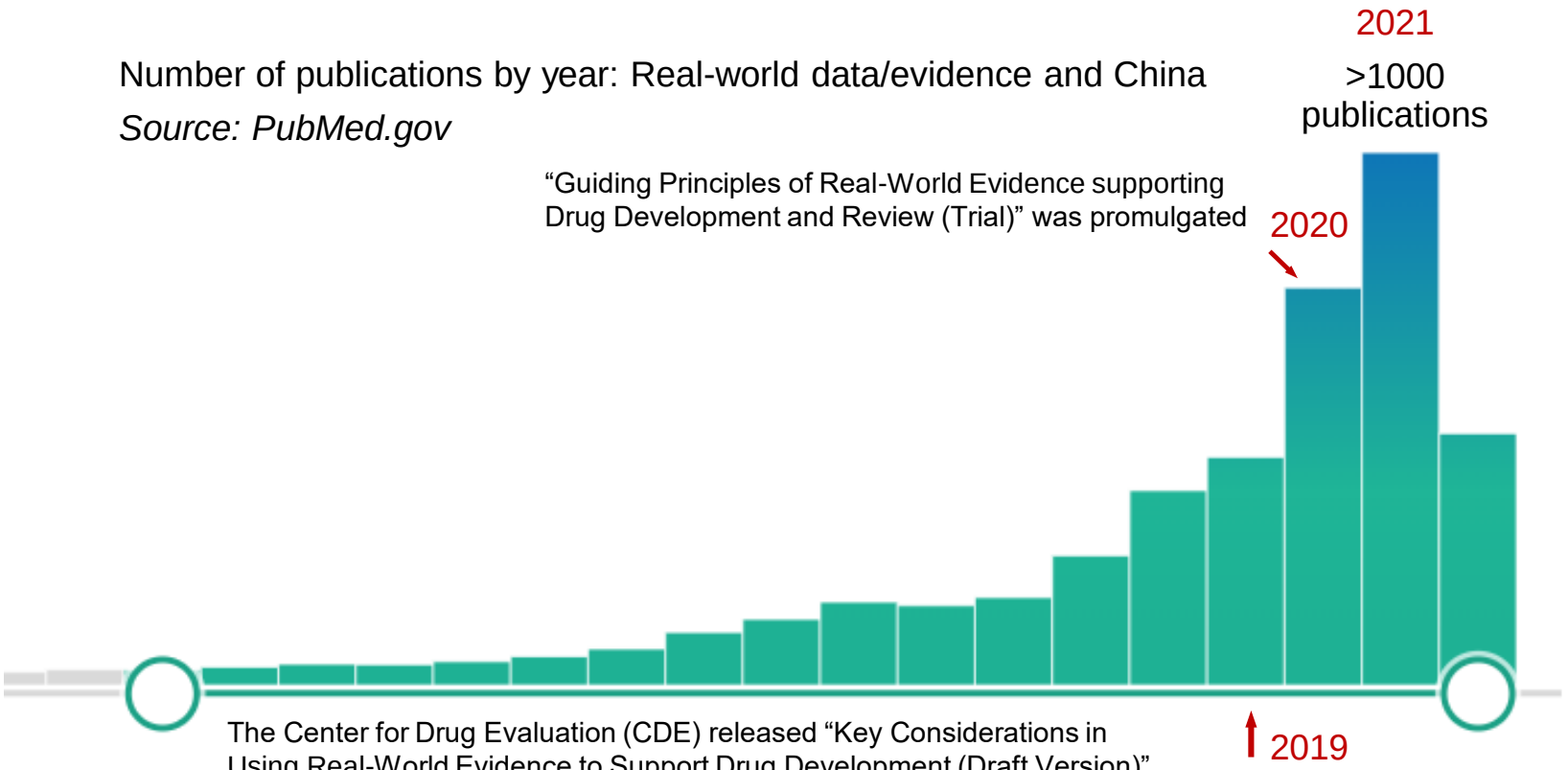
Research-grade real-world data (RWD) is in high demand in China

Strong momentum toward the use of RWE for regulatory purpose

- Fast-track approval opportunities
- Label changes and new indication assessment
- Post-approval assessment and safety surveillance
- Reimbursement decisions
- Clinical practice guidelines

Number of publications by year: Real-world data/evidence and China

Source: PubMed.gov



References:
Xie, J, et al., Real-World Data for Healthcare Research in China: Call for Actions, Value in Health Regional Issues, Volume 27, 72-81
Liang, W, et al., The role of health economics and outcomes research in healthcare reform in China, Pharmacoeconomics. 2014; 32: 231-234
Liu, G, et al., China Guidelines for Pharmacoeconomic Evaluations, China Market Press, Beijing 2020

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Four fundamental challenges in China's RWE research

Innovation and nimbleness are key in addressing data gaps and logistic hurdles

Data quality

- Massive amount of fragmentary data
- Often lacking critical details to inform complete clinical pathway

Data usability

- Rely on manual review and secondary interpretation
- Limited clinical validity in essential clinical endpoints

Timing

- Fast-evolving policies and strategic priorities
- Often need quick turnaround (e.g., to support reimbursement negotiation)

Strategic planning

- Balancing immediate needs and long-term goals
- Factor in government regulations and requirements (e.g., Human Genetic Resource Administration of China (HGRAC))

Example 1: National Longitudinal Cohort of Hematological Diseases in China (NICHE)

Example 2: Aggregate RWD through a facilitated physician survey

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Example 1: National Longitudinal Cohort of Hematological Diseases in China (NICHE)

Innovative solutions for common RWD challenges – an oncology example

Methodology to improve the quality and usability of RWD: An example in acute myeloid leukemia (AML) research

In collaboration with the National Longitudinal Cohort of Hematological Diseases in China (NICHE)

While guidelines for treatment regimens for AML are well known, there is limited knowledge of how patients in China are treated in a real-world setting

The fragmentary data that are lacking **treatment regimen by line** and **patient response** have impeded researchers' ability to use RWE in oncology

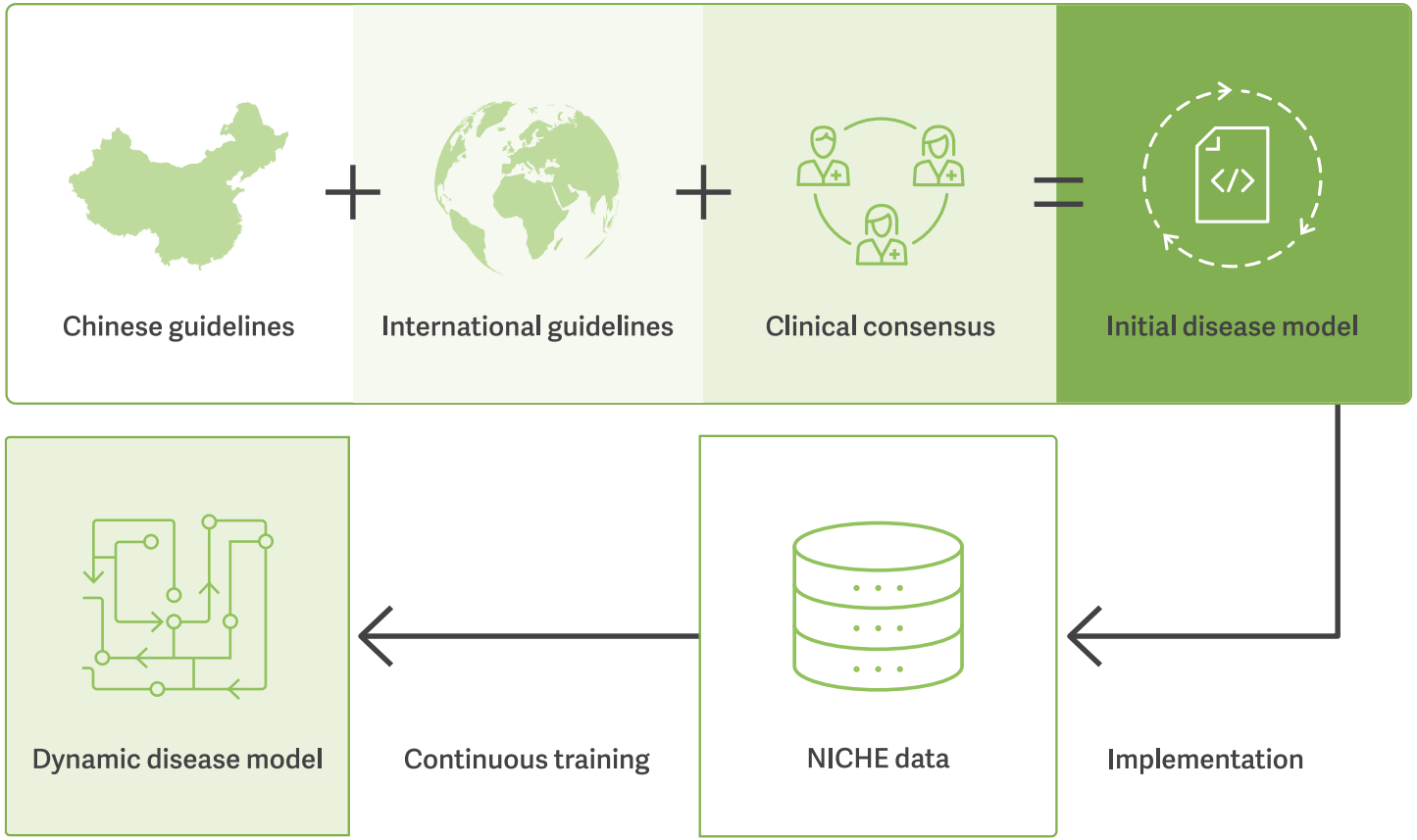
We created algorithms to overcome this gap by using RWE to retrospectively recreate AML patient journeys in China

References:
National Longitudinal Cohort of Hematological Diseases, ClinicalTrials.gov, NCT04645199
Benfa Gong, et.al. Evaluating treatment patterns and outcomes for acute myeloid leukemia in adult patients in China - methodology considerations of RWE, Ninth Southern China Annual Congress on Pharmacoeconomics

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A dynamic, data-driven, and ever-improving disease model

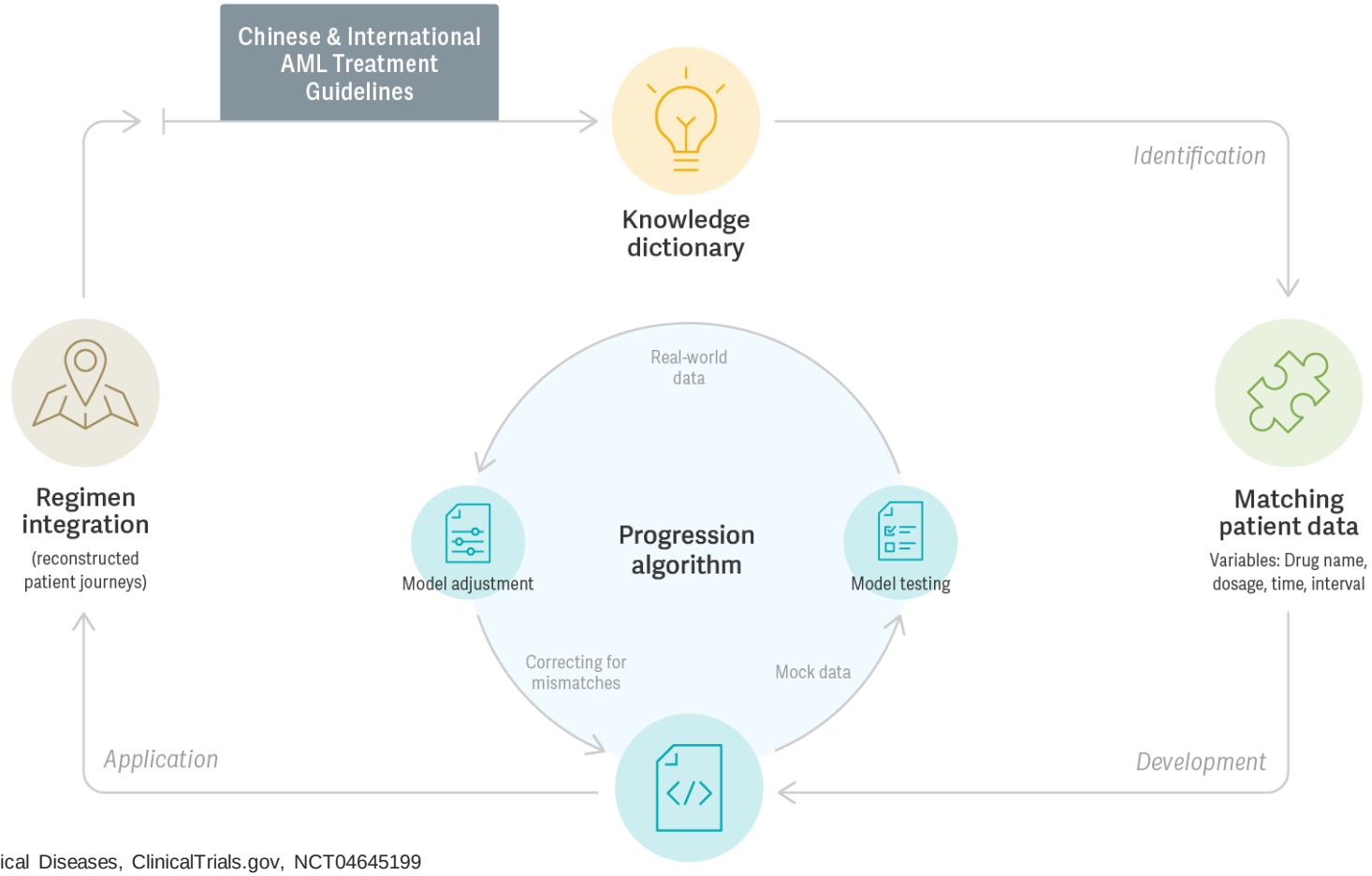
Connecting data, clinical practice, and research



References:
National Longitudinal Cohort of Hematological Diseases, ClinicalTrials.gov, NCT04645199
Benfa Gong, et.al. Evaluating treatment patterns and outcomes for acute myeloid leukemia in adult patients in China - methodology considerations of RWE, Ninth Southern China Annual Congress on Pharmacoeconomics

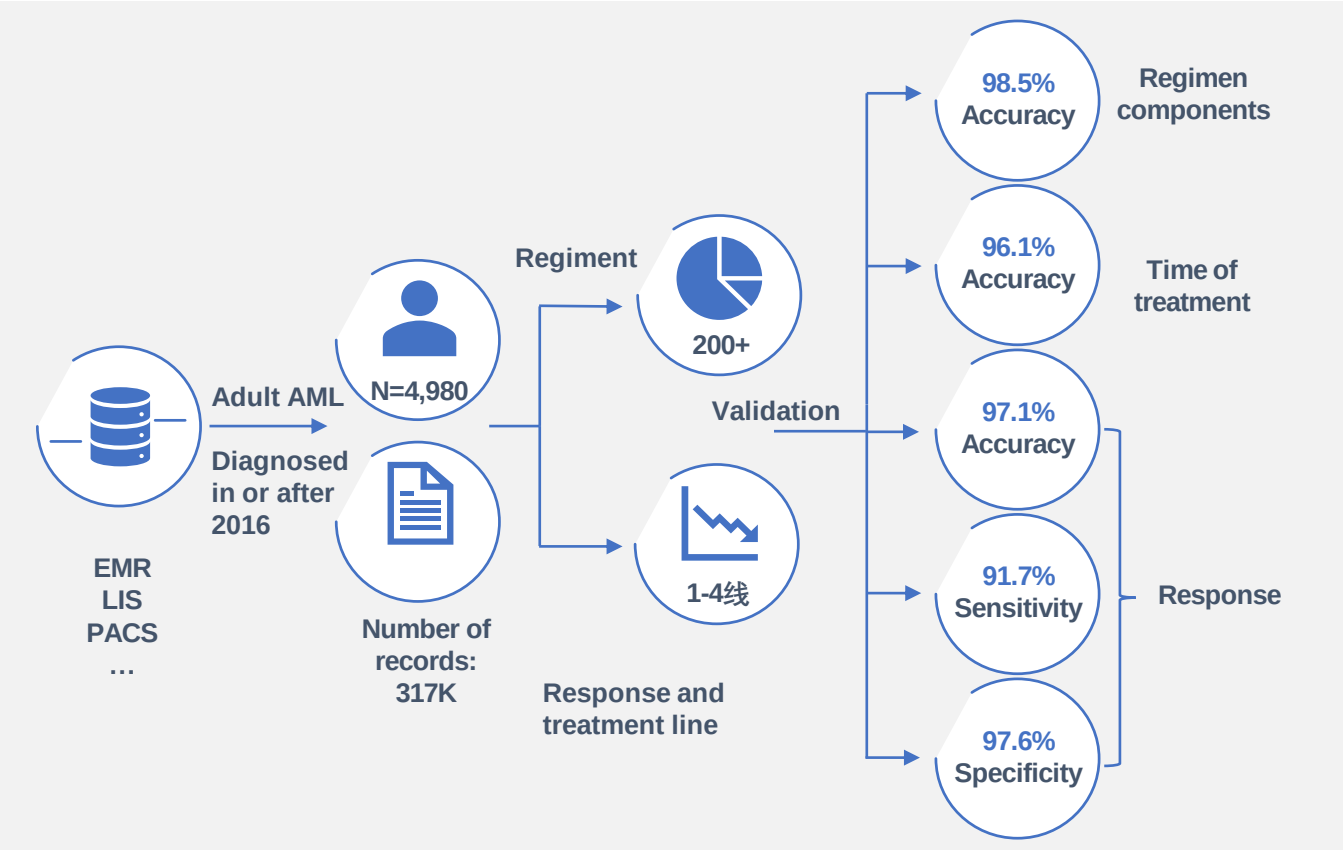
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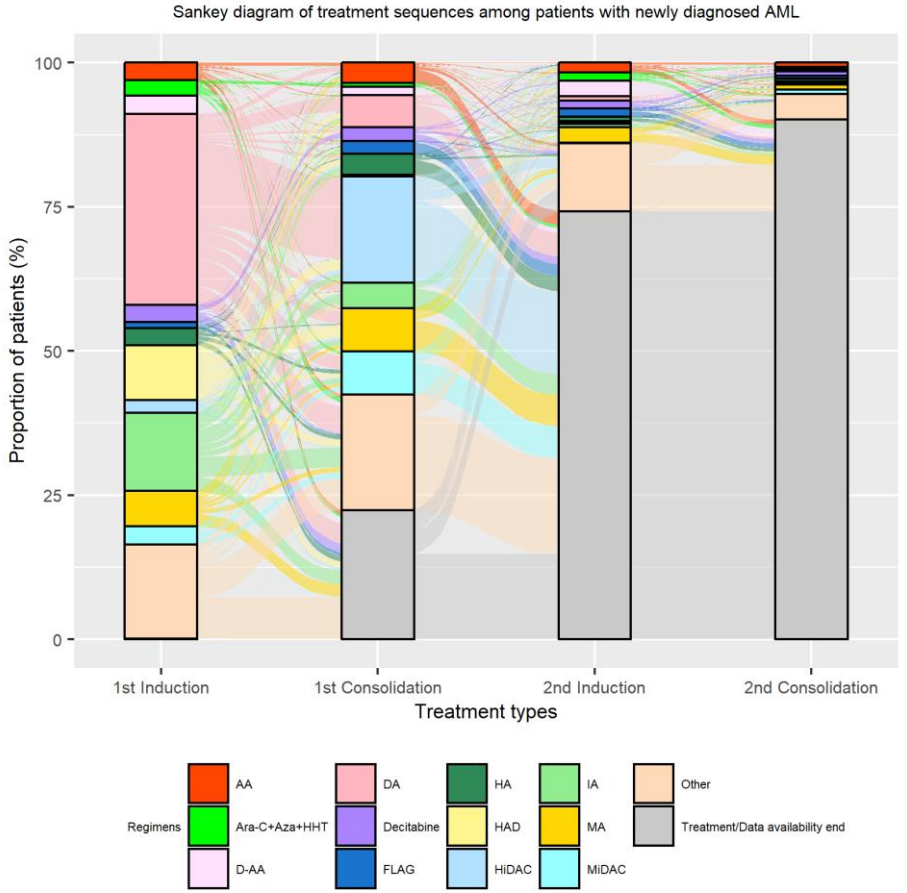
A progression algorithm capable of reconstructing lines of therapy, multi-agent treatment regimens, and treatment responses



References:
National Longitudinal Cohort of Hematological Diseases, ClinicalTrials.gov, NCT04645199
Benfa Gong, et.al. Evaluating treatment patterns and outcomes for acute myeloid leukemia in adult patients in China - methodology considerations of RWE, Ninth Southern China Annual Congress on Pharmacoeconomics

Clinical validation: High accuracy, specificity, and sensitivity





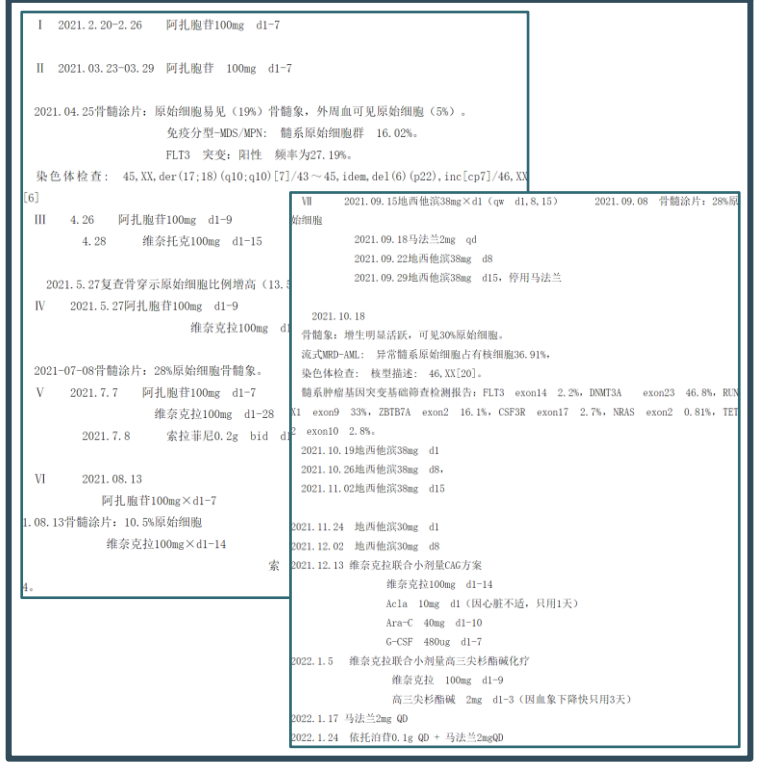
References:
National Longitudinal Cohort of Hematological Diseases, ClinicalTrials.gov, NCT04645199
Benfa Gong, et.al. Evaluating treatment patterns and outcomes for acute myeloid leukemia in adult patients in China - methodology considerations of RWE, Ninth Southern China Annual Congress on Pharmacoeconomics

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Transform historical raw records into a complete picture of the patient journey

Example: mock data from one patient

Unstructured EMR (47 records)



Ⅰ 2021.2.20-2.26 阿扎胞苷100mg d1-7

Ⅱ 2021.03.23-03.29 阿扎胞苷 100mg d1-7

2021.04.25骨髓涂片：原始细胞易见（19%）骨髓象，外周血可见原始细胞（5%）。
免疫分型-MDS/MPN: 髓系原始细胞群 16.02%。
FLT3 突变：阳性 频率为27.19%。
染色体检查： 45,XX,der(17;18)(q10;q10)[7]/43～45,idem,del(6)(p22),inc[cp7]/46,XX
[6]

Ⅲ 4.26 阿扎胞苷100mg d1-9
4.28 维奈托克100mg d1-15

2021.5.27复查骨穿示原始细胞比例增高（13.
Ⅳ 2021.5.27阿扎胞苷100mg d1-9
维奈克拉100mg d

2021-07-08骨髓涂片：28%原始细胞骨髓象。
Ⅴ 2021.7.7 阿扎胞苷100mg d1-7
维奈克拉100mg d1-28
2021.7.8 索拉菲尼0.2g bid d
索
4。

Ⅶ 2021.09.15地西他滨38mg×d1（qw d1,8,15） 2021.09.08 骨髓涂片：28%原始细胞
2021.09.18马法兰2mg qd
2021.09.22地西他滨38mg d8
2021.09.29地西他滨38mg d15，停用马法兰

2021.10.18
骨髓象：增生明显活跃，可见30%原始细胞。
流式MRD-AML: 异常髓系原始细胞占有核细胞36.91%。
染色体检查： 核型描述： 46,XX[20]。
髓系肿瘤基因突变基础筛查检测报告：FLT3 exon14 2.2%，DNMT3A exon23 46.8%，RUN
X1 exon9 33%，ZBTB7A exon2 16.1%，CSF3R exon17 2.7%，NRAS exon2 0.81%，TET
2 exon10 2.8%。
2021.10.19地西他滨38mg d1
2021.10.26地西他滨38mg d8，
2021.11.02地西他滨38mg d15

2021.11.24 地西他滨30mg d1
2021.12.02 地西他滨30mg d8
2021.12.13 维奈克拉联合小剂量CAG方案
维奈克拉100mg d1-14
Acla 10mg d1（因心脏不适，只用1天）
Ara-C 40mg d1-10
G-CSF 480ug d1-7
2022.1.5 维奈克拉联合小剂量高三尖杉酯碱化疗
维奈克拉 100mg d1-9
高三尖杉酯碱 2mg d1-3（因血象下降快只用3天）
2022.1.17 马法兰2mg QD
2022.1.24 依托泊苷0.1g QD + 马法兰2mgQD

Orders (1344 entries)

ORDER_TEXT	DOSAGE	DOSAGE_UNITS	START_DATE_TIME	STOP_DATE_TIME
盐酸利多卡因针(5ml)(华鲁)(*)J	0.10	g	2021-01-14 09:51:10	2021-01-14 09:51:10
盐酸利多卡因针(5ml)(华鲁)(*)J	0.10	g	2021-01-14 09:51:10	2021-01-14 09:51:10
注射用水（10ml)(*)	4.00	ml	2021-02-20 08:30:42	2021-02-20 08:30:42
注射用阿扎胞苷(集采3,**5%,四川)	100.00	mg	2021-02-20 08:30:42	2021-02-20 08:30:42
注射用水（10ml)(*)	4.00	ml	2021-02-20 08:31:18	2021-02-26 08:34:34
注射用阿扎胞苷(集采3,**5%,四川)	100.00	mg	2021-02-20 08:31:18	2021-02-26 08:34:34
托烷司琼针(2mg)(西南)(**)	2.00	mg	2021-02-20 08:31:28	2021-02-20 08:31:28
托烷司琼针(2mg)(西南)(**)	2.00	mg	2021-02-20 08:31:46	2021-02-26 08:34:36
盐酸二甲双胍片(集采3,*,84片,重庆)J	0.25	g	2021-02-20 10:33:33	2021-03-01 10:13:02
单硝酸异山梨酯(鲁南)(*)J	40.00	mg	2021-02-20 10:34:25	2021-03-01 10:13:02
硫酸氢氯吡格雷片	75.00	mg	2021-02-20 10:35:06	2021-03-01 10:13:02
盐酸吡格列酮片	15.00	mg	2021-02-20 10:35:27	2021-03-01 10:13:02
兰索拉唑胶囊(*)	30.00	mg	2021-02-20 10:37:31	2021-03-01 10:13:02
(10mg)阿托伐他汀钙片(集采1,*,齐鲁)J	20.00	mg	2021-02-21 08:28:52	2021-03-01 10:13:02
艾司唑仑片(倍谊)(*)J	1.00	mg	2021-02-21 09:26:25	2021-02-21 09:26:25
艾司唑仑片(倍谊)(*)J	1.00	mg	2021-02-22 08:54:58	2021-02-22 08:54:58
艾司唑仑片(倍谊)(*)J	1.00	mg	2021-02-24 09:13:25	2021-02-24 09:13:25
开塞露(20ml)(金虹)(*)J	100.00	ml	2021-02-24 09:13:29	2021-02-24 09:13:29
粒细胞集落刺激因子(300ug)(双鹭)(**)	300.00	ug	2021-02-24 10:54:47	2021-02-24 10:54:47
艾司唑仑片(倍谊)(*)J	1.00	mg	2021-02-26 08:52:16	2021-02-26 08:52:16
粒细胞集落刺激因子(300ug)(双鹭)(**)	300.00	ug	2021-02-26 08:59:34	2021-02-26 08:59:34
粒细胞集落刺激因子(300ug)(双鹭)(**)	300.00	ug	2021-02-27 08:23:50	2021-02-27 08:23:50
艾司唑仑片(倍谊)(*)J	1.00	mg	2021-02-27 08:24:01	2021-02-27 08:24:01
粒细胞集落刺激因子(300ug)(双鹭)(**)	300.00	ug	2021-02-28 11:35:11	2021-02-28 11:35:11
0.9%氯化钠注射液（500ml)(软袋）(*)J	500.00	ml	2021-02-28 15:20:17	2021-02-28 15:20:17
粒细胞集落刺激因子(300ug)(双鹭)(**)	300.00	ug	2021-03-01 08:29:51	2021-03-01 08:29:51
注射用水（10ml)(*)	4.00	ml	2021-03-23 09:10:42	2021-03-23 09:10:42
注射用阿扎胞苷(集采3,**5%,四川)	100.00	mg	2021-03-23 09:10:42	2021-03-23 09:10:42
注射用水（10ml)(*)	4.00	ml	2021-03-23 09:11:04	2021-03-29 07:56:17
注射用阿扎胞苷(集采3,**5%,四川)	100.00	mg	2021-03-23 09:11:04	2021-03-29 07:56:17

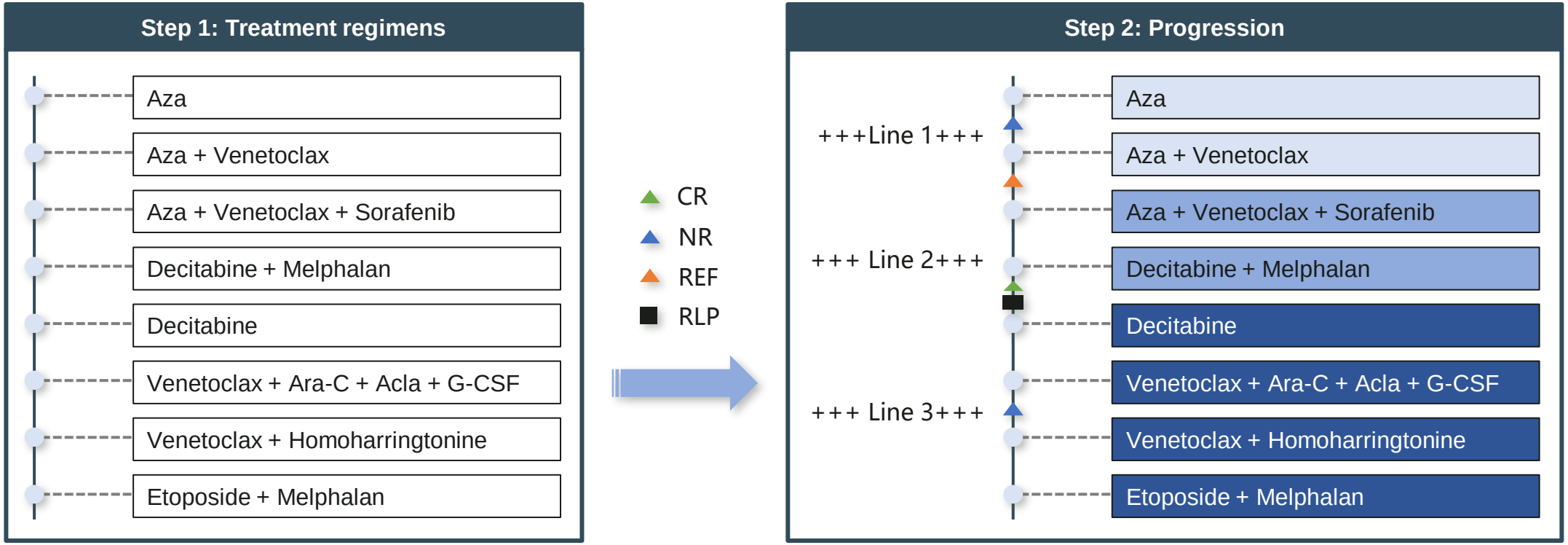
Lab tests (5259 entries)

specimen	item_name	report_item_name	result
静脉血	血细胞分析（住院静脉血+分类+网织④	平均红细胞体积-MCV	101.5
静脉血	血细胞分析（住院静脉血+分类+网织④	白细胞-WBC	0.57
静脉血	血细胞分析（住院静脉血+分类+网织④	红细胞-RBC	2.6
静脉血	血细胞分析（住院静脉血+分类+网织④	血红蛋白-HGB	96
静脉血	血细胞分析（住院静脉血+分类+网织④	红细胞压积-HCT	26.4
静脉血	血细胞分析（住院静脉血+分类+网织④	平均红细胞血红蛋白含量-MCH	36.9
静脉血	血细胞分析（住院静脉血+分类+网织④	平均红细胞血红蛋白浓度-MCHC	364
静脉血	血细胞分析（住院静脉血+分类+网织④	血小板-PLT	66
静脉血	血细胞分析（住院静脉血+分类+网织④	淋巴细胞比例-LYMPH%	75.4
静脉血	血细胞分析（住院静脉血+分类+网织④	单核细胞比例-MONO%	0
静脉血	血细胞分析（住院静脉血+分类+网织④	嗜中性粒细胞比例-NEUT%	22.8
静脉血	血细胞分析（住院静脉血+分类+网织④	嗜酸性粒细胞比例-EO%	0
静脉血	血细胞分析（住院静脉血+分类+网织④	嗜碱性粒细胞比例-BASO%	1.8
静脉血	血细胞分析（住院静脉血+分类+网织④	淋巴细胞绝对值-LYMPH#	0.43
静脉血	血细胞分析（住院静脉血+分类+网织④	单核细胞绝对值-MONO#	0
静脉血	血细胞分析（住院静脉血+分类+网织④	嗜中性粒细胞绝对值-NEUT#	0.13
骨髓	染色体核型分析（R带+G带）	核型描述:	46,XY[15]
骨髓	染色体核型分析（R带+G带）	备注：	R+G带
骨髓	染色体荧光原位杂交MLL	描述	nuc ish(MLL×2)
骨髓	染色体荧光原位杂交MLL	采用探针	双色MLL(3’ MLL红色/5’ MLL绿色)
骨髓	染色体荧光原位杂交MLL	阈值	<2.17%
骨髓	染色体荧光原位杂交MLL	计数细胞类型	间期细胞
骨髓	染色体荧光原位杂交MLL	计数细胞数量	500
骨髓	染色体荧光原位杂交MLL	阳性信号百分率	0.8%
静脉血	Rh血型鉴定[RhD(O)]-全自动	Rh血型	+(阳性)
静脉血	Rh血型鉴定[RhD(O)]-全自动	Anti-D	4+
骨髓	骨髓组织细胞化学染色三项含瑞染+像	特异性酯酶(CE)阳性指数	NA
骨髓	白血病40种融合基因筛查实验	白血病相关融合基因筛查结论	送检标本中融合基因阴性或低于检测灵敏度。

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Transform historical raw records into a complete picture of the patient journey

Example: mock data from one patient

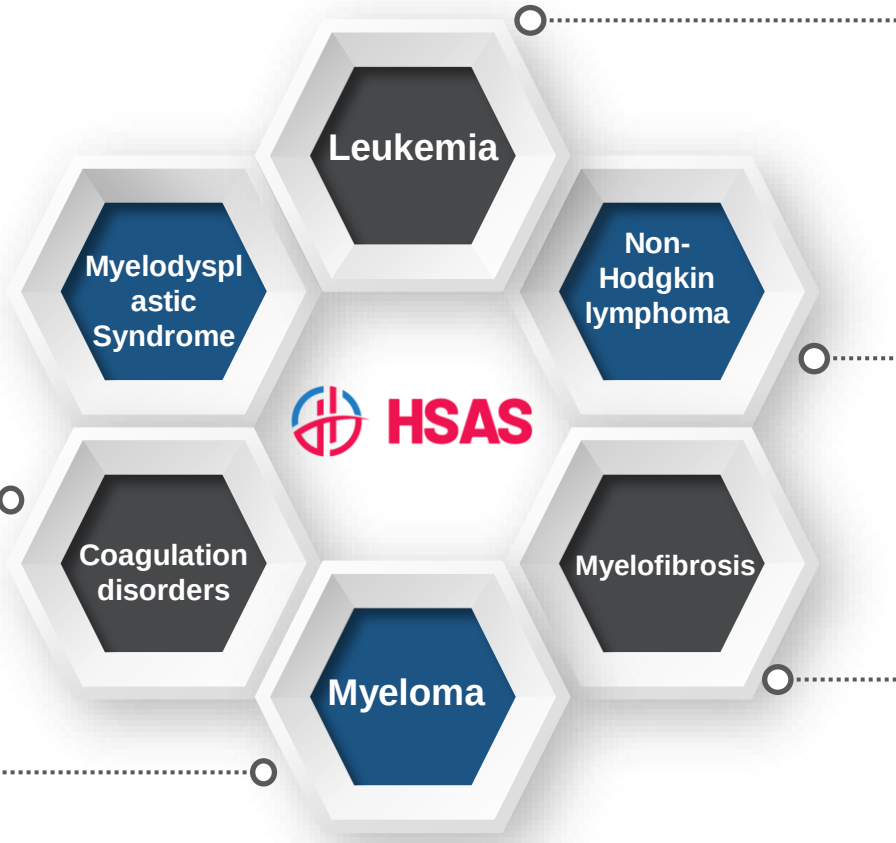


Abbreviations: CR, complete remission; NR, no remission; REF, refractory; RLP, relapse.

References:
AML response criteria – CIBMTR forms instruction manual. https://www.cibmtr.org/manuals/fim/1/en/topic/aml-response-criteria
Ma, J. 中国复发难治性急性髓系白血病诊疗指南(2021年版).中华血液学杂志2021年8月第42卷第8期 Chinese Journal of Hematology, August 2021, Vol. 42, No. 8
Benfa Gong, et.al. Evaluating treatment patterns and outcomes for acute myeloid leukemia in adult patients in China - methodology considerations of RWE, Ninth Southern China Annual Congress on Pharmacoeconomics

Application in a variety of hematological conditions

Implemented through the Huashu Hematology Medical information management System (HHMS)



- Acute myeloid leukemia (AML)
- Acute promyelocytic leukemia (APL)
- Acute lymphoblastic leukemia (ALL)
- Chronic myelogenous leukemia (CML)
- …

- Hemophilia A
- Hemophilia B
- Hemophilia C

- Diffuse large B-cell lymphoma (DLBCL)
- Mantle cell lymphoma (MCL)
- Follicular lymphoma (FL)
- Marginal zone lymphoma (MZL)
- …

- Multiple myeloma (MM)
- Smoldering multiple myeloma (SMM)

- Primary myelofibrosis
- Secondary myelofibrosis

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Example 2: Aggregate RWD through a facilitated physician survey

A nimble alterative to generate early and reliable evidence under logistic constraints

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Generate timely and reliable RWE to support market access in China

Background

- Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare condition associated with substantial disease burden
- Evidence based on local data is warranted to support regulatory and formulary milestones
- Generating RWD for rare conditions is typically resource intensive and time consuming
  - Only 7 months to close the RWD gap
  - Institutional review board (IRB) and HGRAC approvals take 6-8 months, limiting feasibility of primary data generation such as panel-based chart review studies and multi-center analysis

Key considerations

- Health care resource allocation is centralized in China, especially in rare conditions, and the number of physicians highly experienced in EGPA management is limited
- Early key opinion leader engagement is critical in market access (e.g., reimbursement, hospital inventory listing) in China
- An efficient strategy should also serve as a feasibility assessment to facilitate future RWE initiative and formulate research questions

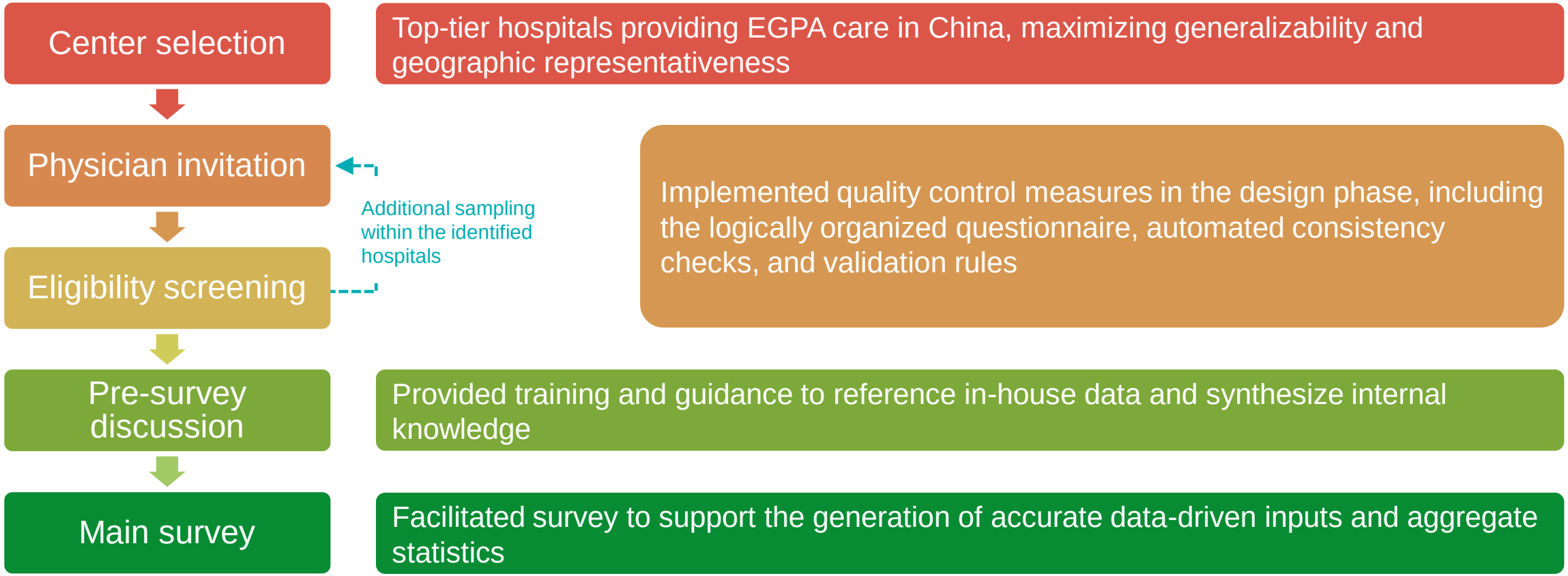
Solutions

This aggregate RWD study based on a facilitated survey aims to understand the disease burden due to EGPA in China, based on top tertiary hospitals' experience

References:
https://www.uptodate.com/contents/epidemiology-pathogenesis-and-pathology-of-eosinophilic-granulomatosis-with-polyangiitis-churg-strauss
https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-eosinophilic-granulomatosis-with-polyangiitis-churg-strauss
https://www.uptodate.com/contents/treatment-and-prognosis-of-eosinophilic-granulomatosis-with-polyangiitis-churg-strauss

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A facilitated survey of 16 physicians from 14 top hospitals



Reference:
ISPOR abstract 214662: Clinical Manifestations and Health Care Resource Utilization of Eosinophilic Granulomatosis with Polyangiitis (EGPA) in China: A Cross-Sectional Multi-Center Physician Survey Study, Session 3: Tuesday, May 17 from 12:15-1:15pm EST

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Study population

Physician population (N=16)

Physicians' department, N (%):
Pulmonology/respiratory care: **4 (25.0)** Rheumatology: **12 (75.0)**

Physicians' title, N (%)
Chief physician: **10 (62.5)** Associate chief physician: **5 (31.2)**
Attending physician: **1 (6.2)**

Years in practice, N (%):
11–20 years: **7 (43.8)** >20 years: **9 (56.2)**

Patients with EGPA treated by each physician in the past 12 months
Median (range): **8.5 (3.0, 36.0)**

Patients with R/R disease per physician‡

Median (range): **3.0 (1.0, 20.0)**

Patients with corticosteroid-dependent disease per physician§

Median (range): **3.0 (1.0, 36.0)**

Patient population underlying the reported statistics

Aggregated data from **243** patients with EGPA*

Age of patients at EGPA diagnosis, years, median (range): **45.3 (35.0, 60.0)**

Male patients, %, median (range): **46.0 (20.0, 75.0)**

Organs involved at diagnosis, %:
Lung: **80.0**
Respiratory tract: **66.7**
Sino-nasal: **53.3**

EGPA-related conditions at diagnosis, %, median (range)†:
Eosinophilia: **100.0 (40.0, 100.0)**
Asthma: **94.0 (33.3, 100.0)**

Disease duration, years, median (range): **14.5 (10.0, 30.0)**

Duration from asthma diagnosis to EGPA diagnosis, years, median (range): **4.4 (0.5, 15.0)**

Reference:
ISPOR abstract 214662: Clinical Manifestations and Health Care Resource Utilization of Eosinophilic Granulomatosis with Polyangiitis (EGPA) in China: A Cross-Sectional Multi-Center Physician Survey Study, Session 3: Tuesday, May 17 from 12:15-1:15pm EST

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Disease burden through the lens of physician-reported aggregate data

Clinical manifestations	All patients*	Patients with R/R disease*†	Patients with corticosteroid-dependent disease*†
Ever achieved remission, %, median (range)	85.0 (60.0, 100.0)	-	57.1 (25.0, 100.0)
Currently in remission, %, median (range)	71.4 (50.0, 100.0)	-	42.9 (0.0, 80.0)
Average time from treatment to remission, years, median (range)	0.5 (0.1, 3.0)	-	0.8 (0.3, 3.0)
Ever experienced relapse, %, median (range)	40.0 (18.2, 60.0)	-	60.0 (22.2, 100.0)
With vasculitis activity and damage, %, median (range) Proportion of patients with FFS=1 Proportion of patients with FFS≥2	50.0 (0.0, 100.0) 40.0 (0.0, 60.0) 45.0 (0.0, 80.0)	80.0 (0.0, 100.0) 30.0 (0.0, 50.0) 60.0 (0.0, 100.0)	80.0 (0.0, 100.0) 30.0 (0.0, 50.0) 60.0 (0.0, 100.0)

Our findings were consistent with the literature and other studies based on patient-level data in China:

- 王芊霖, 嗜酸性肉芽肿性多血管炎患者临床特征及生存分析, 北京协和医学院硕士毕业论文
- Chen Y, Guo X, Zhou J, et al. Cardiac involvement in eosinophilic granulomatosis with polyangiitis: A retrospective study in the Chinese population. Frontiers in Medicine. 2020;7:583944.
- EGPA expert consensus writing committee. Multidisciplinary expert consensus on the diagnosis and treatment of eosinophilic granulomatous polyangiitis. Chinese Journal of Tuberculosis and Respiratory Medicine. 2018;41(007):514-521.

Reference:
ISPOR abstract 214662: Clinical Manifestations and Health Care Resource Utilization of Eosinophilic Granulomatosis with Polyangiitis (EGPA) in China: A Cross-Sectional Multi-Center Physician Survey Study, Session 3: Tuesday, May 17 from 12:15-1:15pm EST

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An efficient approach to supplement multi-center real-world patient-level analyses and generate timely RWE under logistic constraints

	A: Physician survey	B: Multi-center real-world study
Strengths	▪ Provides valuable insights on multiple dimensions ▪ Draws on experience from top hospitals (e.g., 20-40 centers) and maximizes generalizability through center selection across regions ▪ A cost-effective approach with a shorter study timeline ▪ Can serve as a feasibility assessment for B, while independently addressing other objectives	▪ Patient-level data from hospital information system will be available to support more detailed data investigation ▪ Enables in-depth analyses such as associational analysis ▪ Higher scientific rigor and evidence weight ▪ Establishes foundation for long-term collaborations with leading institutions
Limitations	▪ Relies on physician-reported patient data at an aggregate level ▪ Some data fields might be subject to recall bias/reporter bias. Measures are taken during the design phase to minimize these concerns, and guidance and support are essential to ensure data quality	▪ More time consuming and resource intensive compared to A ▪ Early planning is important to factor in IRB and HGRAC approval timelines ▪ Does not provide physician perspectives

Reference:
ISPOR abstract 214662: Clinical Manifestations and Health Care Resource Utilization of Eosinophilic Granulomatosis with Polyangiitis (EGPA) in China: A Cross-Sectional Multi-Center Physician Survey Study, Session 3: Tuesday, May 17 from 12:15-1:15pm EST

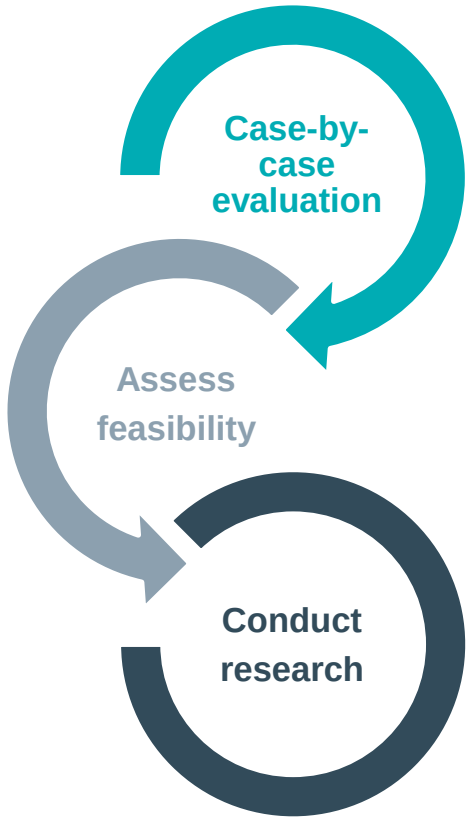
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General recommendations for generating RWE in China

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Building the RWD foundation to support both short-term and long-term goals

Each study has a unique optimal design and approach



Formulate strategy for evidence generation

A road map of tangible actions that aligns well with launch milestones, short-term objectives, and long-term development

Establish collaboration

Early planning with clinician inputs to support launch and reimbursement will pinpoint key issues and maximize downstream efficiency

Develop a sustainable RWD framework

Lay a strong research foundation to optimize data value for stakeholders, strengthen data scope, and integrate different data sources over time



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Part III – Practical Experience in Utilizing Real-world And Clinical Trial Data for Assessing Treatment Effects

L. J. Wei, PhD

Professor of Biostatistics, Harvard University

Two groups of patients (real world and clinical trial)

- These two groups of patients can be quite different.
- What is the estimand (target population; endpoints; treatment contrast)?
- Are endpoint assessments similar between two groups?
- What is the index time (time zero) for patient in the real-world setting (via repeated biomarkers to define index time)?
- What are the baseline variables?
- How to select patients in the RW matching those in the trial (the target is the trial population)?
- How to make further adjustments?

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Various methods for adjustments

- Matching “baseline” covariates
- Propensity score matching
- Inverse probability treatment weighting
- Outcome regression (not ANCOVA)
- Bayesian dynamic borrowing (model-free treatment contrast?)
- Entropy balancing (weighting individual patient)
- Double robustness

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In theory, it seems not a big deal for borrowing information from RW data, but in reality…..

- Two real examples (single arm and RWD)

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Circulation: Cardiovascular Quality and Outcomes (2019)

Integrating Data From Randomized Controlled Trials and Observational Studies to Assess Survival in Rare Diseases Insights From Pulmonary Arterial Hypertension

By A. Torbicki, MD et al.

(Hajime Uno at DFCI; Maria Bacchi and Brian Hennessy, Actelion → JnJ)

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SERAPHIN
A global, multicenter RCT with macitentan in PA

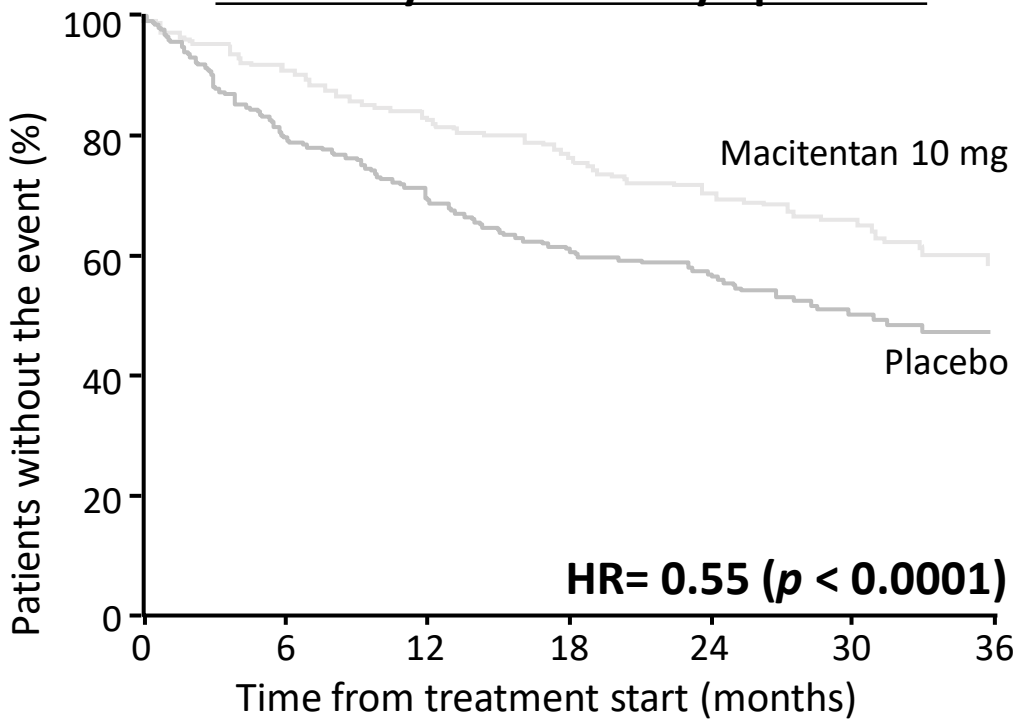
A global, double-blind, randomized, placebo-controlled trial

- Patients were randomized (1:1:1) to placebo, macitentan 3 mg, or macitentan 10 mg.
- The primary end point was the time from the initiation of treatment to the first occurrence of a composite end point of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, or worsening of pulmonary arterial hypertension.
- A total of 250 patients were randomly assigned to placebo, 250 to 3-mg, and 242 to the 10-mg. The hazard ratio for the 10-mg vs placebo was 0.55 (97.5% CI, 0.39 to 0.76; P<0.001).

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SERAPHIN: Primary & secondary endpoints

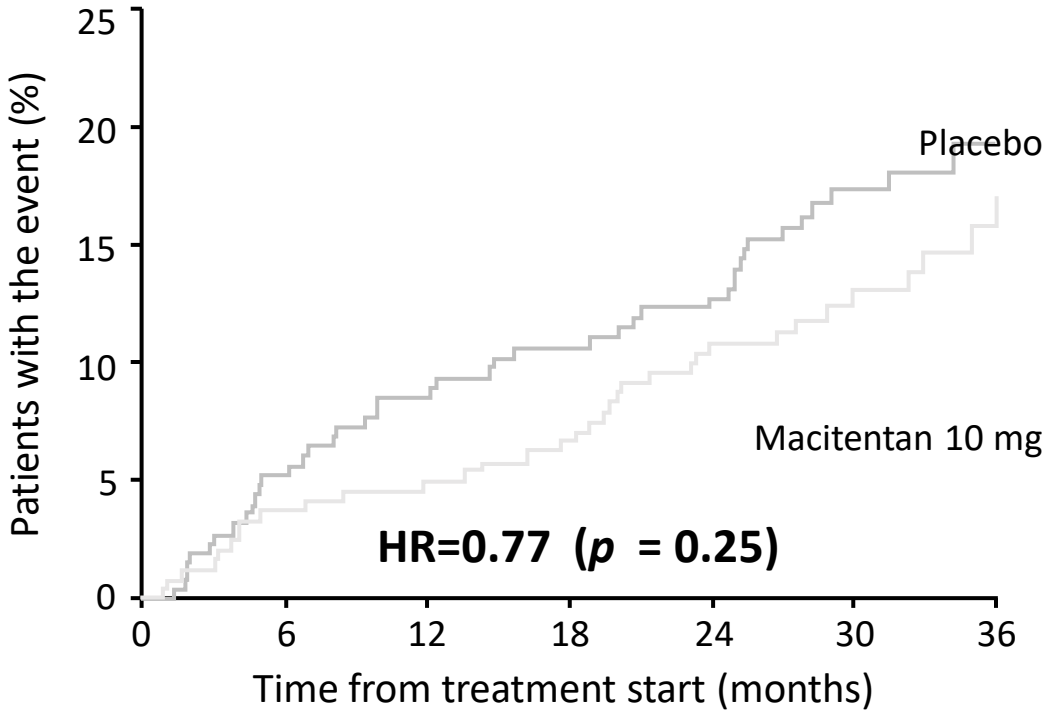
Morbidity and mortality up to EOT



Patients at risk

Macitentan 10 mg	242	208	187	171	155	91	41
Placebo	250	188	160	135	122	64	23

All-cause mortality up to EOS



Patients at risk

Placebo	242	230	225	221	211	132	63
Macitentan 10 mg	250	231	219	214	208	124	51

EOS: end of study; EOT: end of treatment

Pulido T, et al. N Engl J Med 2013; 369: 809-18.

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How about survival benefit?

- Some of the patients in the control arm were crossed over to the treated arms after experiencing non-fatal primary events.
- It is difficult to conduct a trial with respect to survival endpoint.
- Could we use external data to assess if the treatment had survival benefit?

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REVEAL Registry Study for PAH

- REVEAL
  - A US-based, multicenter registry of patients designed to provide information on the demographics, clinical course and management of 3515 patients with PAH

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Challenges of using external controls

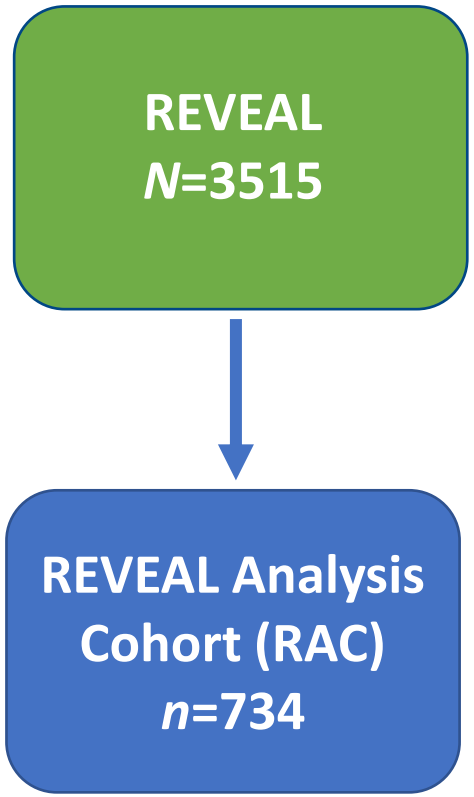
- REVEAL enrolled a broader population of PAH patients than SERAPHIN for disease classification, severity, and age et al.

- Need to select a cohort of REVEAL patients who could have been enrolled in SERAPHIN

- The final cohort selection variables were based on SERAPHIN inclusion and exclusion criteria.

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Selection of REVEAL Cohort



SERAPHIN RCT eligibility criteria

- ≥ 12 years
- WHO FC I-IV*
- PAH confirmed by RHC:
  - mPAP > 25 mmHg
  - PCWP ≤ 15 mmHg
  - PVR > 320 dyn·sec·cm^{-5}
- IPAH, HPAH or related to: CTD, simple corrected congenital shunts, HIV or drug/toxin exposure
- 6MWD ≥ 50 m
- Body weight ≥ 40 kg
- SBP ≥ 100 mg
- Estimated creatinine clearance ≥ 30 mL/min

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Baseline characteristics: RAC and SERAPHIN populations

Variable	SERAPHIN Placebo n= 250	SERAPHIN Macitentan 10 mg n= 242	REVEAL RAC n = 734
Female, %	74.0	80.2	81.1
Age, years	46.8 (17.1)	45.5 (15.0)	52.3 (14.7)
SBP, mmHg	115.6 (13.5)	116.3 (14.1)	120.3 (14.9)
Heart rate, bpm	79.3 (12.1)	77.8 (12.1)	84.0 (14.7)
BMI, kg/m2	25.1 (5.1)	25.6 (6.1)	28.8 (6.4)
SVO2, %	64.8 (8.8)	64.5 (9.7)	62.8 (9.5)
PVR, dyn·sec·cm-5	995 (783.3)	1040 (672.5)	888 (520)
mRAP, mmHg	8.8 (5.6)	9.2 (6.0)	9.1 (5.5)
Borg Index	3.5 (2.1)	3.5 (2.3)	3.1 (2.0)
6MWD, m	352 (110.9)	363 (93.2)	369 (125.2)
WHO functional class, %			
I	0	0.4	7.6
II	52.0	49.6	35.8
III	46.4	47.9	51.4
IV	1.6	2.1	5.2

All data are mean (SD) unless otherwise stated. *REVEAL RAC v SERAPHIN Maci 10 mg. RAC: REVEAL analysis cohort

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To further refine the comparability

- Building a survival prediction model using REVEAL data with the baseline covariates
- Initially, 29 covariates were considered from REVEAL;11 not available in SERAPHIN;18 covariates were used for modelling building.

- Predicting survival for each SERAPHIN patient using this model
- Getting the average of those 742 survival curves
- Comparing this average predicted survival with the survival observed in the SERAPHIN trial

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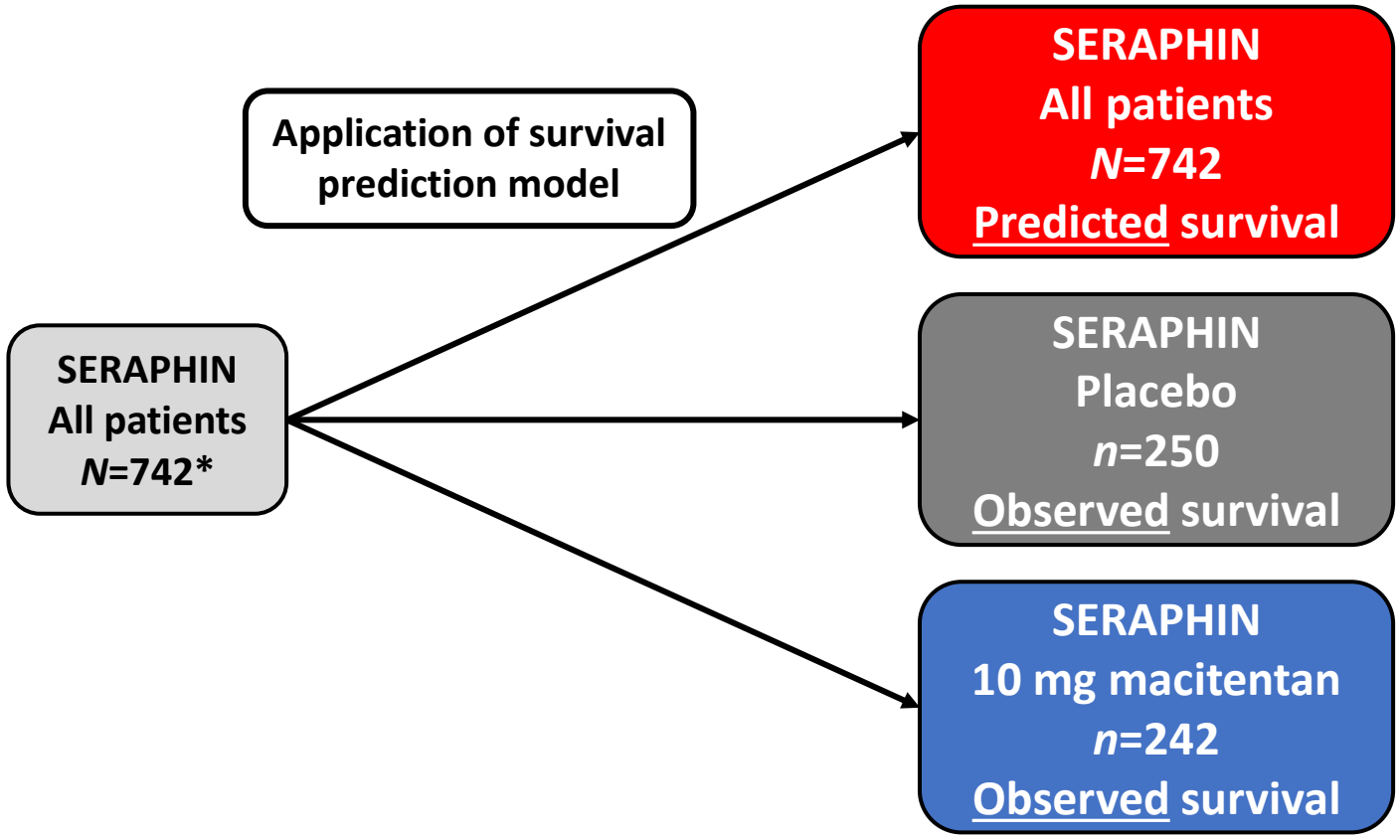
Variables retained for the prediction model

Variable	Hazard ratio	95% CI	*P* value
WHO FC: II vs. I	1.15	0.44–99	0.782
WHO FC: III vs. I	2.14	0.86–37	0.103
WHO FC: IV vs. I	4.14	1.50–43	0.006
PAH: Idiopathic vs. Familial	0.59	0.35–98	0.043
PAH: CTD vs. Familial	1.30	0.77–18	0.322
6MWD: 165–439m vs. < 165m	0.51	0.33–78	0.002
6MWD: ≥ 440 m vs. < 165 m			<0.001
Age: 58–82 yrs vs. < 58 yrs			0.018
Age: > 83 yrs vs. < 58 yrs			0.006
Male vs. Female	1.95	1.33–84	0.001
BMI kg/m^2	0.96	0.93–99	0.007
Heart Rate > 92 bpm	1.40	0.98–00	0.068
SBP < 110 mmHg	2.05	1.44–91	<0.001
Borg Score: 5–7 vs. ≤ 4	1.51	1.00–27	0.050
Borg Sore: ≥ 8 vs. ≤ 4	2.99	1.63–48	<0.001
SVO_2 < 60%	1.84	1.30–62	0.001

C statistic = .76

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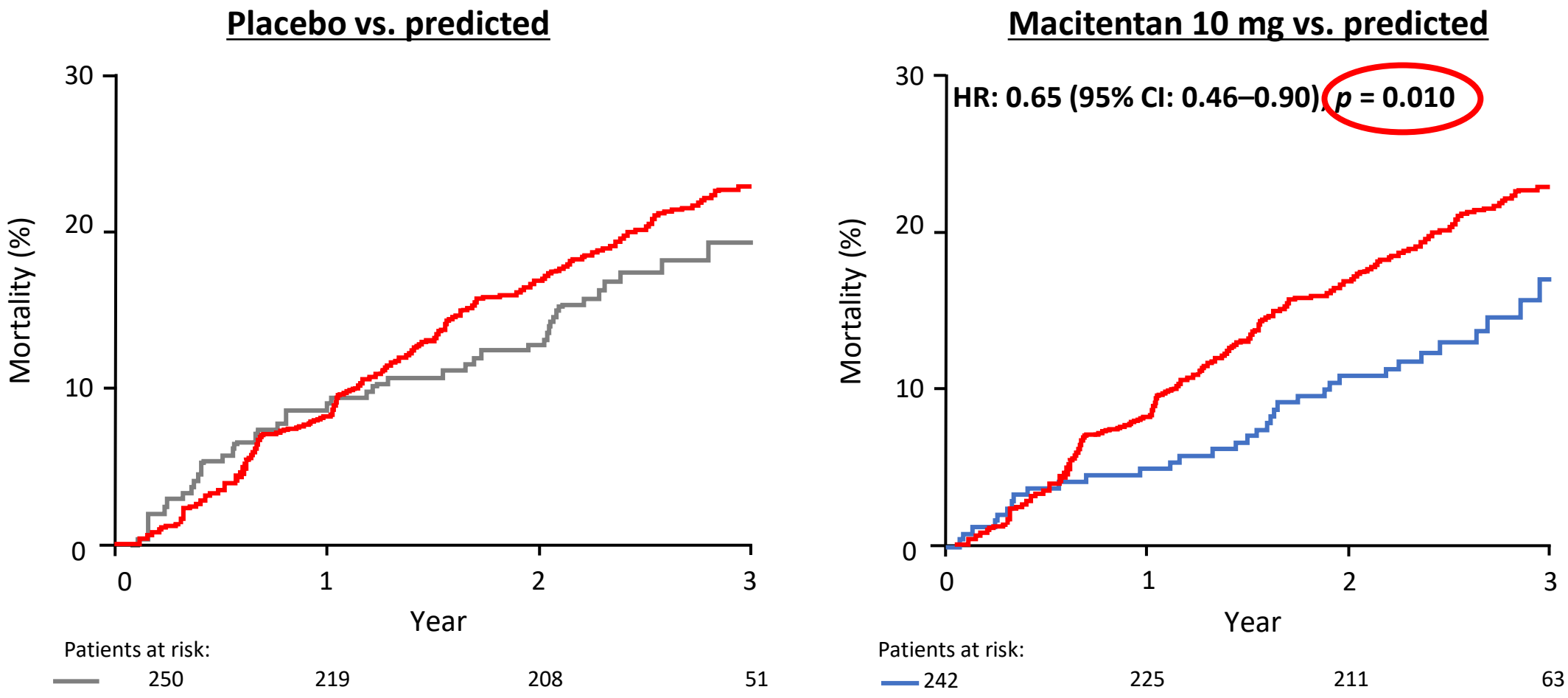
Application of the prediction model to patients enrolled in SERAPHIN



In the SERAPHIN study patients were randomised to placebo (n=250), macitentan 3 mg (n=250) and macitentan 10 mg (n=242).

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Time to all-cause death up to 3 years



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How to obtain hazard ratio from the predicted survival curve?

- For the predicted curve, we sampled a large number observations and compared them with the survival data from trial arm to get HR estimate.
- Using the standard bootstrapping to get confidence intervals for the hazard ratio
- Using the area under the curve as a summary of the survival curve is much less computing intensive.

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Limitations

- These analyses were not pre-specified and are therefore subject to the usual caveats of post-hoc analyses
- Unknown confounders that could lead to differences in risk of mortality are not accounted for
- Is the predicted model ok for the trial population?
- How about “soft” endpoints?

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- In a setting of a rare disease where evaluating mortality is extremely challenging, using real-world and RCT data can bring valuable insights,
- The risk of mortality was underestimated in the observed SERAPHIN placebo arm due to cross-over to active therapy.
- The risk of mortality observed with macitentan 10 mg in SERAPHIN was 35% lower than the predicted mortality for all patients in SERAPHIN.
- Outcome regression method is intuitive and flexible for choosing the target population (not for PS or IPTW).
- If there were data from “pure” placebo in the trial, we may check the model fitting.

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Overall survival with oral selinexor plus low-dose dexamethasone versus real-world therapy in triple-class-refractory multiple myeloma

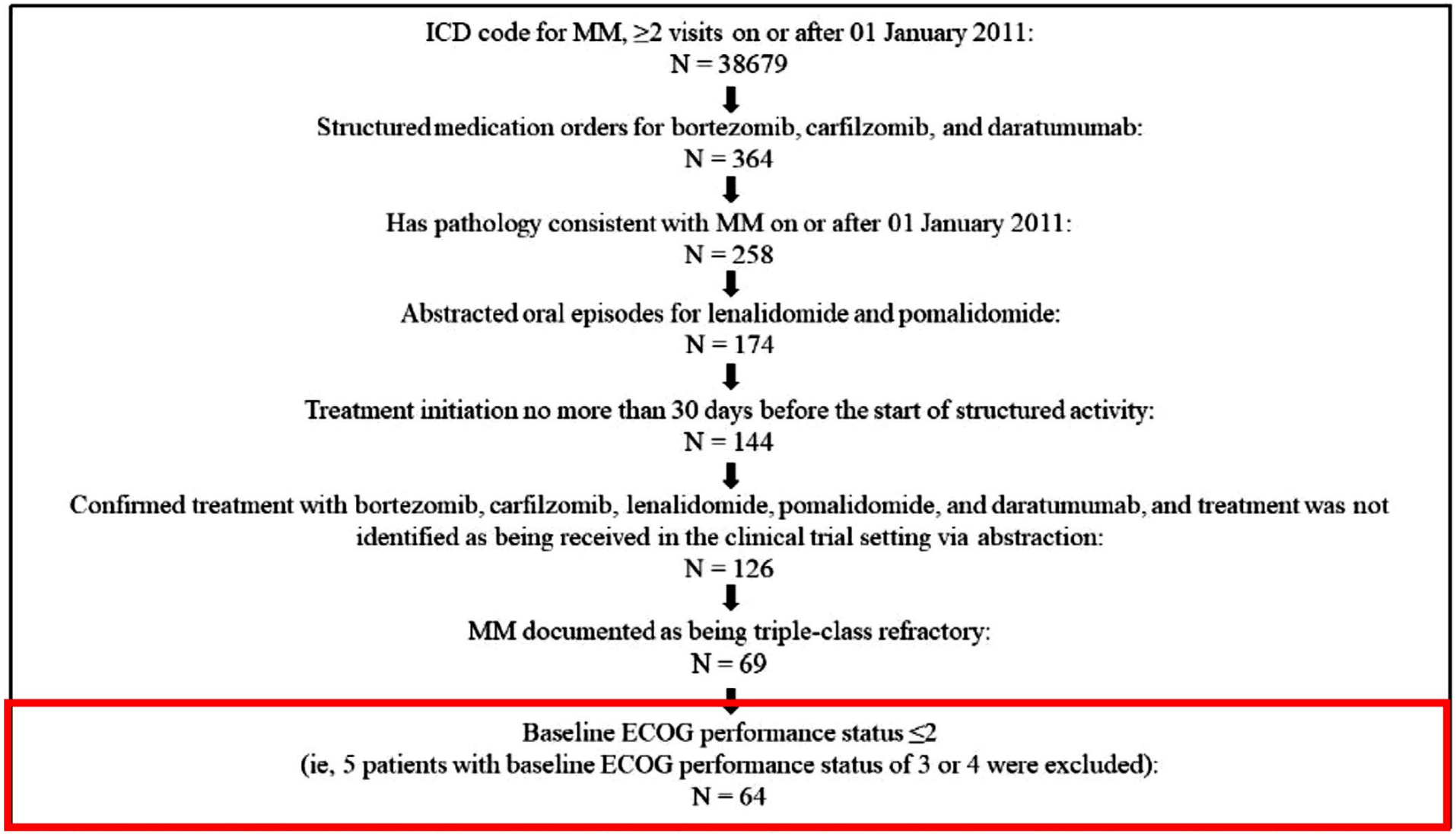
Paul G. Richardson (eJHaem, British Society for Haematology) 2020

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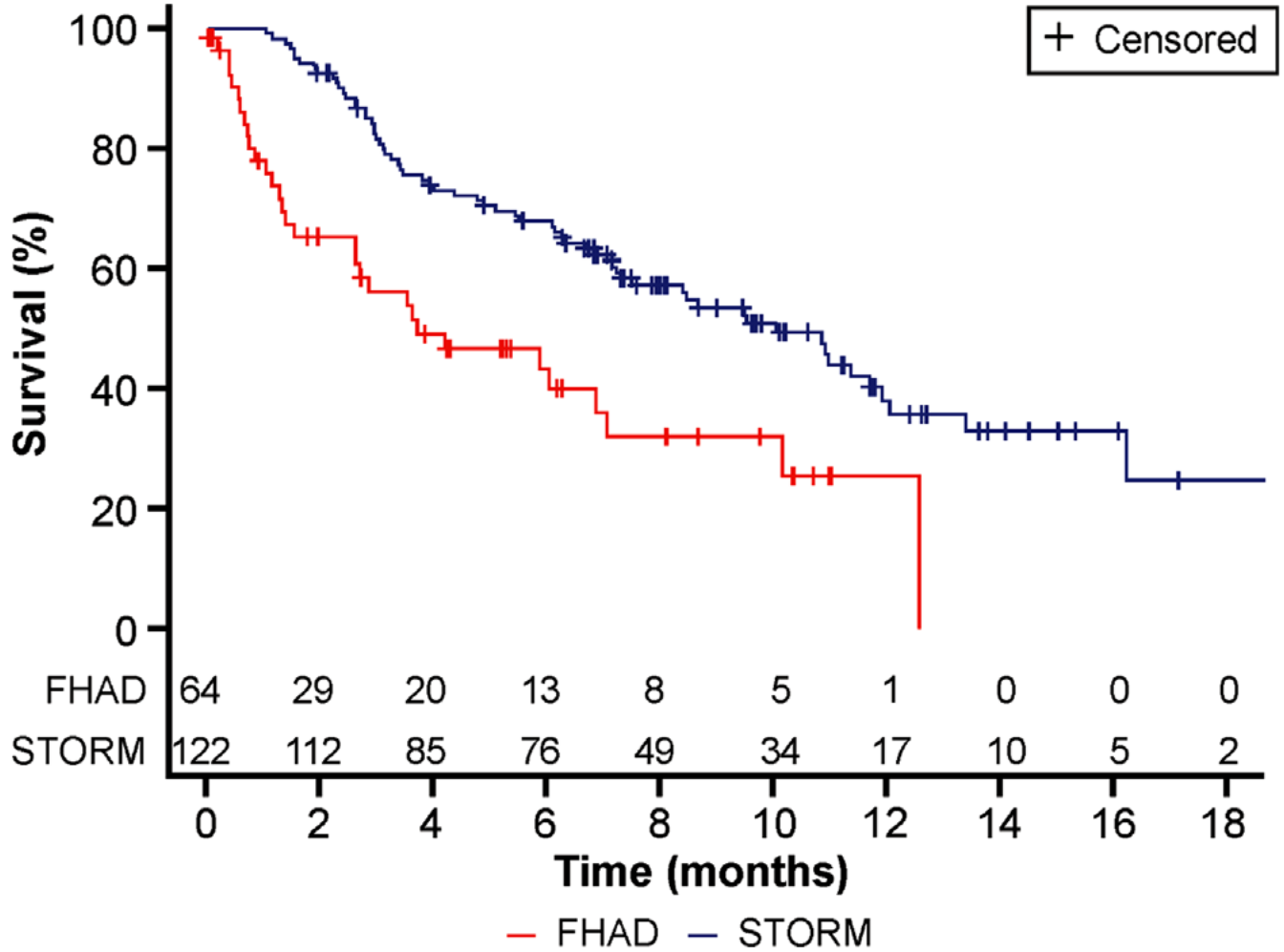
Triple-class-refractory multiple myeloma (MM)

- Patients had proteasome inhibitors, immunomodulatory agents, and anti-CD38 monoclonal antibodies.
- STORM study was a phase 2 with one arm: oral selinexor plus low-dose dexamethasone (Sel-dex)
- The response rate was 26.2%.
- How about overall survival benefit? Where could we get the “controls?”
- With the OS from 122 patients in the trial and 64 similar patients treated with other available therapies in a Flatiron Health Analytic Database (FHAD) cohort, OS was longer for patients with Selinexor; with hazard ratio 0.43 (P = .0002) and adjusted HR 0.35 (P = .011).

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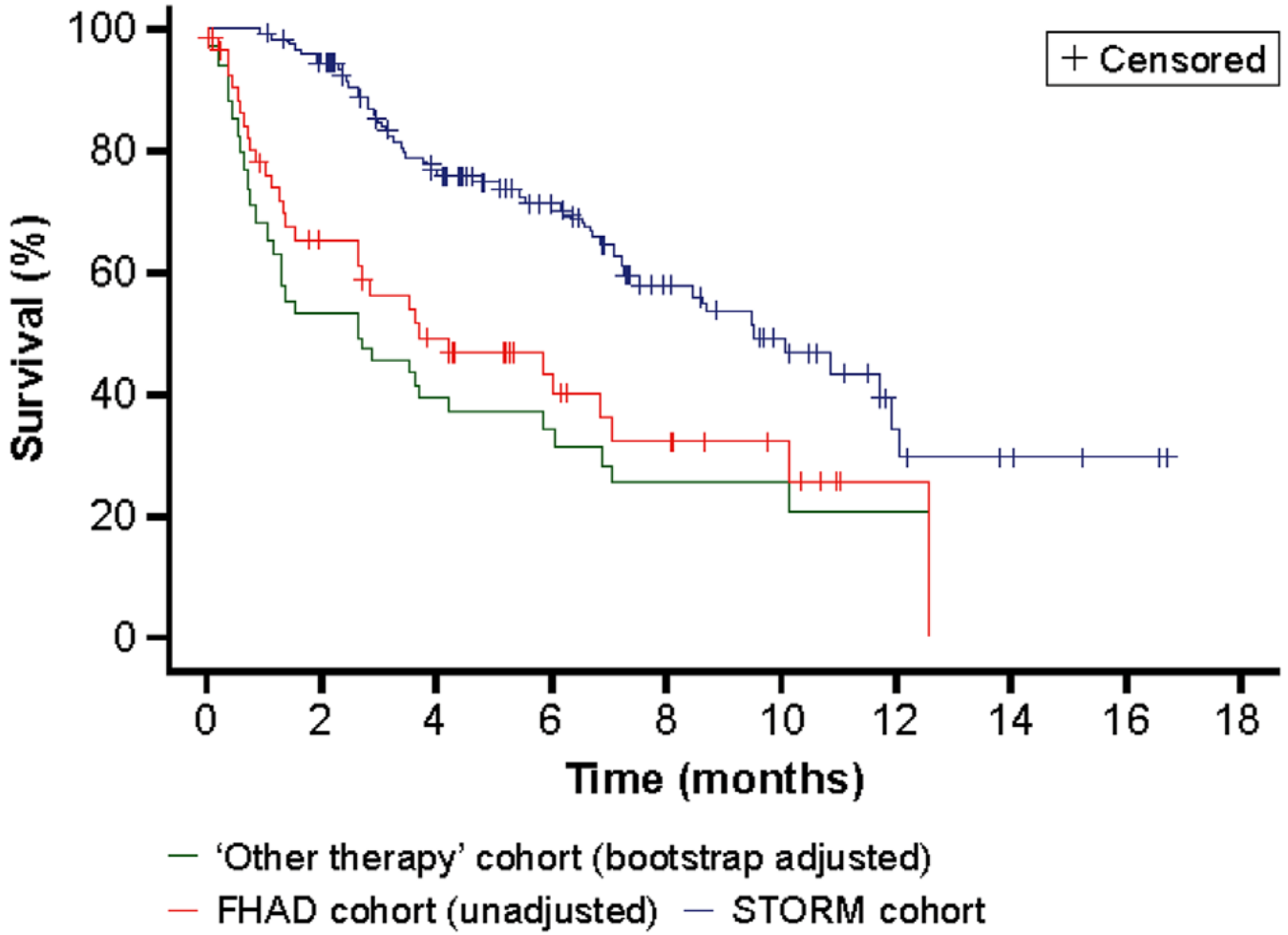


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Unadjusted OS in the overall analysis (STORM vs FHAD cohort). HR= 0.43 (p=0.0002)

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Adjusted OS using predictive modeling in the overall analysis. FHAD. HR =0.35, p=0.011

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Conclusions

- Outcome regression seems intuitive and interpretable
- It provides survival curve estimate directly.
- If we have data from the control in the clinical study, we can then check the adequacy of the model.
- Need pre-specified analysis plan
- Designing a trial using RWD

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