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Real-Life Data in Drug Development

GetReal WP2 – Live Broadcast
Introduction to the concept of drivers of effectiveness

April 18th, 2016

3 – 4.30pm, UK time

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Real-Life Data in Drug Development

PRESENTERS

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Laser Analytica

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Questions?

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Introduction to the GetReal Project

Chris Chinn, Sanofi

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GetReal® Consortium

- GetReal: “Incorporating real-life clinical data into drug development strategies”
- Launched by the *Innovative Medicines Initiative* (IMI), the Europe's largest **public-private** initiative
- 32 public and private partners
- 3-year project with a budget of 17M euros

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Context of the GetReal project

- There is an Efficacy-Effectiveness Gap resulting in persistence of unmet medical needs, even with development of new products
  - This gap can be accurately assessed or decreased if approximation of effectiveness can be done during / as part of drug development rather than post-authorization
- Earlier estimation of efficacy-effectiveness continuum will increase the likelihood of realizing the full potential of the impact of new pharmaceutical product on patients, right from the time of approval

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Context of the GetReal project

- A new paradigm is key to success in this evolving environment
  - To leverage payer input earlier and often to develop compelling, payer-relevant value propositions
  - To reduce the gap between “the bench and bedside”
  - To demonstrate real-world and comparative effectiveness
  - To identify and target patient sub-populations that will maximize effectiveness and value for patients
  - To improve adherence, compliance and Health outcomes
  - To proactively assess and address safety concerns & relative benefit/ risk assessments

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Objectives of GetReal

- To investigate how and when Effectiveness research can be incorporated into R&D drug development plans
  - To identify or develop study designs and analytical tools for pragmatic/ effectiveness estimation before launch, and develop standards
  - To develop a Decision-Making Framework to facilitate the assessment, and aid in the design of alternative development strategies that provide evidence of relative effectiveness

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Overview of Navigator

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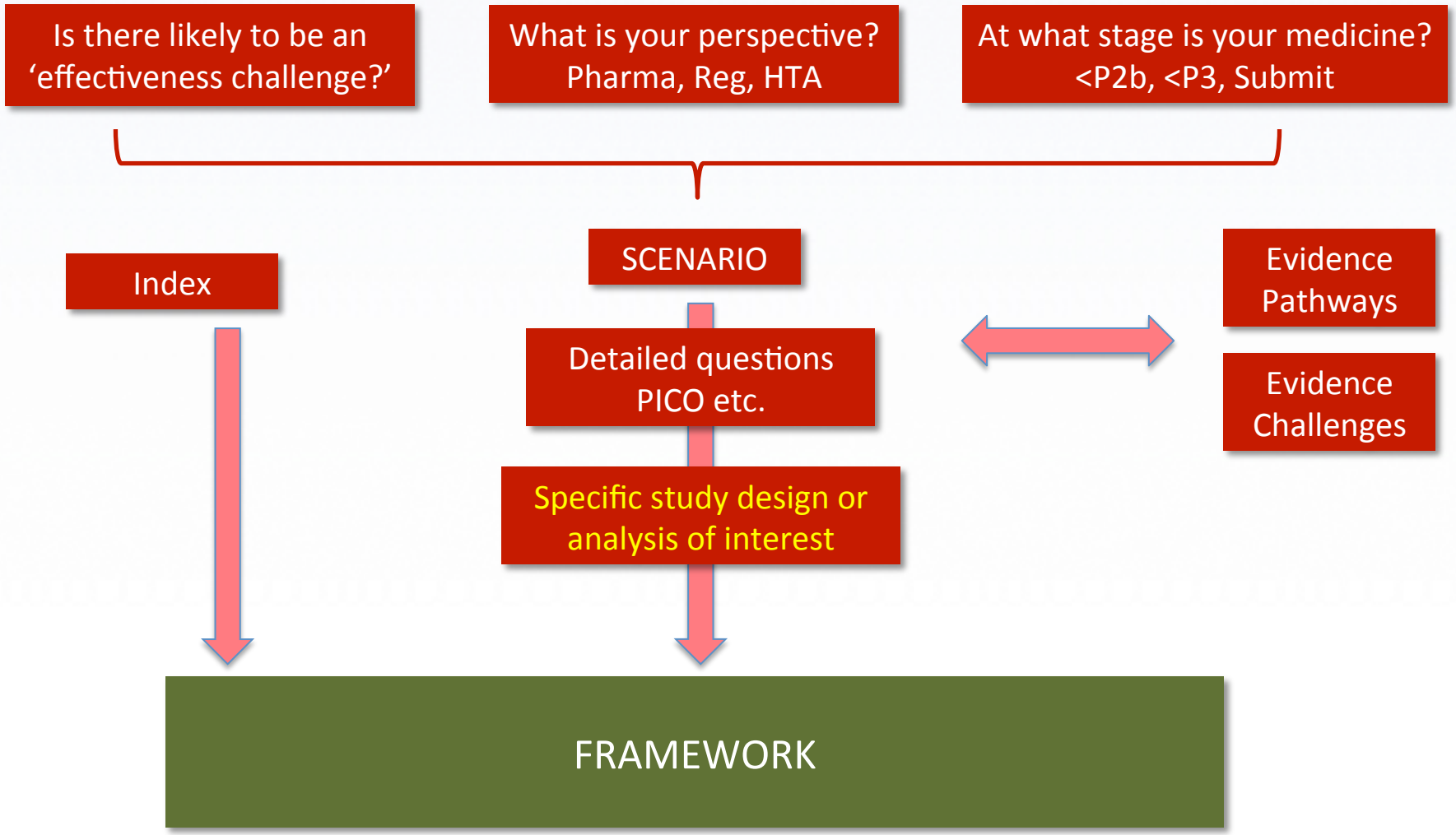

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GetReal organisation

- WP 1: to develop a common framework for the assessment of relative effectiveness (between Regulatory, Pharma R&D, HTA, academics)
- **WP 2: to provide different possible options of designs for pre-authorization studies to assess Relative Effectiveness**
- WP 3: to address operational aspects of conducting pre-authorization pragmatic clinical trials
- WP 4: to synthesize evidence and provide predictive modeling tools
- WP 5: Project Management and dissemination

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Real-Life Data in Drug Development

The concept of drivers of effectiveness

Professor Lucien Abenhaim, LASER Analytica

Honorary Professor, London School of Hygiene and Tropical Medicine

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Questions

1. What drivers of effectiveness to consider?
2. Can you find them in the literature?
3. Can you identify them before launch from existing observational data?
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From the conceptual to the operational approach

- In order to develop innovative study designs / analytical tools to better assess the effectiveness of drugs prior to their market authorization, one needs to
  - Better understand **what is effectiveness**
  - Develop a conceptual framework, to **anticipate** a potential efficacy-effectiveness gap in order to tackle this soon enough
  - And then identify adequate solutions

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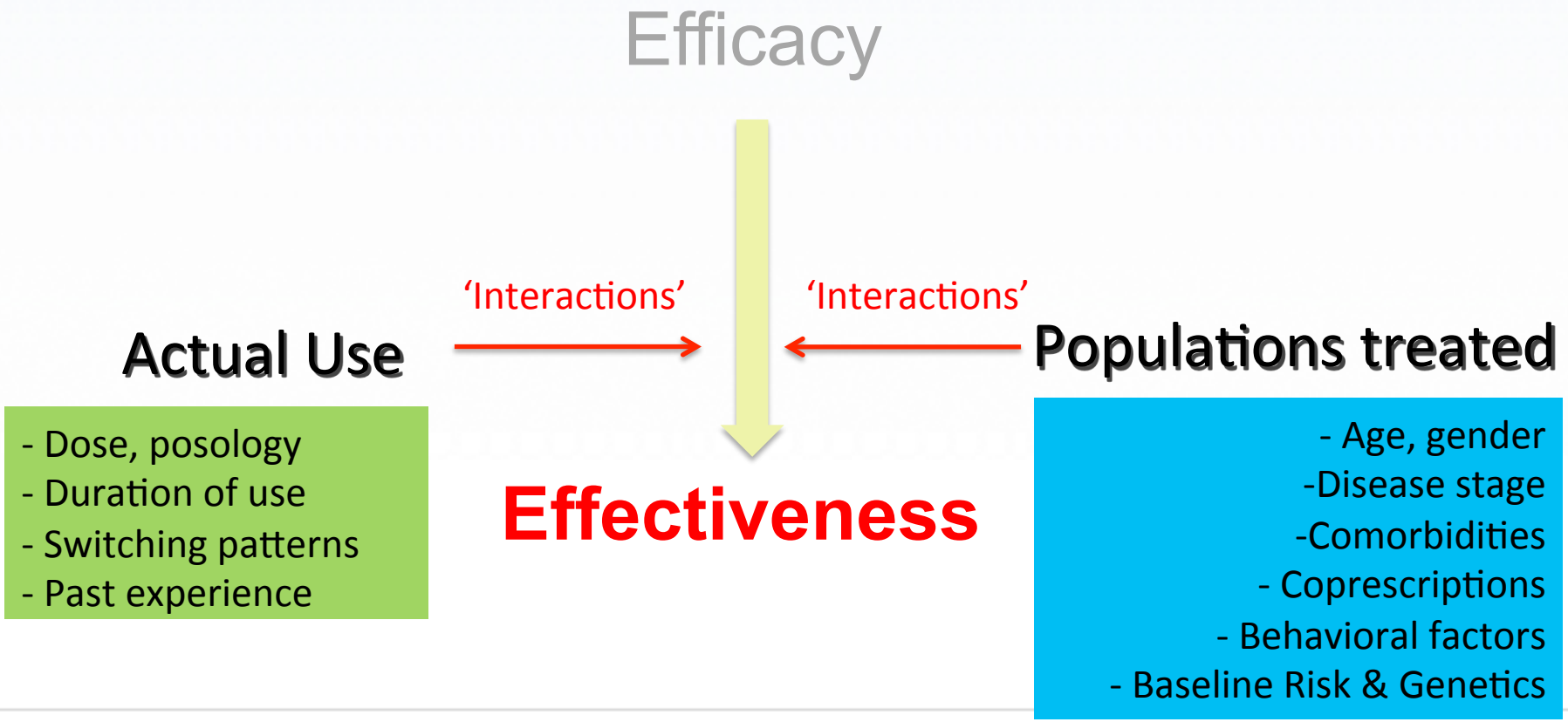
Effectiveness: the impact of drug efficacy when all "interactions" are at play



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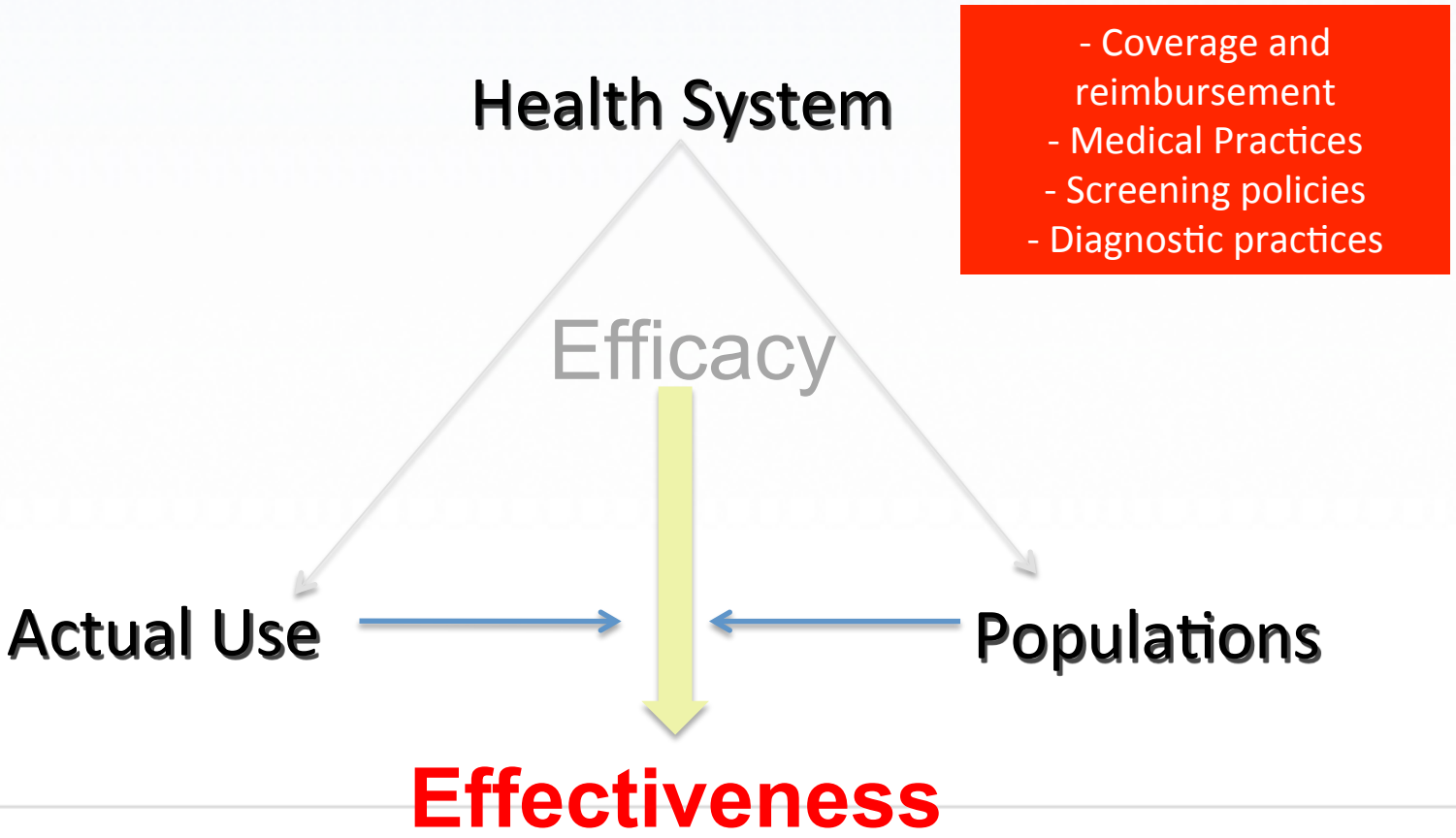
- Actual use and populations exposed are also dependable on practices and health systems



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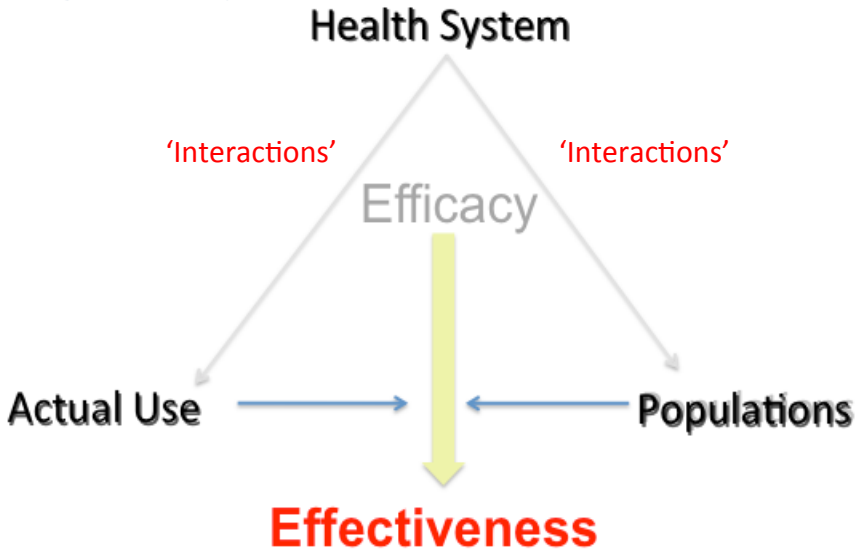
Conceptual approach

- The purpose of Effectiveness Research is to assess these "interactions":
  - Which ones are "universal"
  - How do they distribute locally
  - What is the magnitude of their impact
  - What is the mechanism of Action
- This covers the entire span of epidemiologic and public health research methods



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Operational approach

- Drivers of effectiveness
  - DoE are key "effect modifiers" which will account for a difference between efficacy effect estimate and the effectiveness effect estimate ("efficacy-effectiveness gap")
- The present Research Framework holds that
  - Drivers of effectiveness may be identified early during the drug development process
  - The use of information on these drivers of effectiveness may help narrow the gap between efficacy and effectiveness

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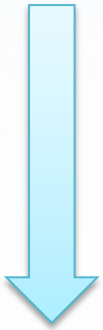
Operational approach

- How can we IDENTIFY drivers of effectiveness?



- How can we IMPLEMENT drivers of effectiveness?

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Methods to identify drivers of effectiveness

Clémentine Nordon, LASER Analytica

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Questions

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Methods to identify drivers of effectiveness

- 3 types of methods
  - Literature-based approach
  - Expertise-based approach
  - Data-based approach

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1. Literature review to identify drivers of effectiveness

Drivers of effectiveness	Hodgkin Lymphoma	Schizophrenia
Population characteristics		
Age	Yes (> 60-70)	No
Gender	No	Yes
Ethnicity	No	Yes
BMI	No	No
Duration of disease	No	Yes (<3-5 years)
Lifetime or current severity of disease	Yes	Yes
Comorbidities	Yes	Yes (e.g., drug use)
Actual drug use		
Treatment toxicity	Yes	-
Adherence	No	No

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2. Experts interviews to identify drivers of effectiveness

Factors to be considered as potential drivers of antipsychotics effectiveness (SCZ)	Agreement between experts
Cannabis (THC) use	Cited by 3 experts
Adherence / level of insight	Cited by 2 experts
Negative schizophrenia symptoms	Cited by 2 experts
Substance (Psychostimulants) abuse	Cited by 2 experts
Severity at onset	Cited by 1 expert
Staging (disease chronicity)	Cited by 1 expert
Nicotine use	Cited by 1 expert

- Overall
  - Useful but not very specific

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Conclusions on LR and experts interviews

- Literature Review / Experts interviews should be used as preliminary step, mainly to generate hypothesis before analysing data
- Limitations
  - LR are limited to what was already explored/reported
    - The absence of results does not mean there are no driver of effectiveness
  - LR may also be limited by the quality of studies
  - LR cannot study interactions, correlations etc.. between factors if those are not included in the publication

3. Data analyses to identify drivers of effectiveness (SCZ)

- What type of data?
  - Patient-level data
  - The more naturalistic the better
    - Heterogeneity is a good thing
  - The more informative, the better
    - Patients characteristics, lifestyle
    - Actual drug use
    - Setting characteristics
  - Type of "effectiveness" needs to be specified
    - "Absolute" effectiveness? (no comparison)
    - Relative/comparative effectiveness ?

e-Health Care Database may be limited …

And cohort study data are difficult to find

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3. Data analyses to identify drivers of effectiveness

On 2 observational datasets in schizophrenia (CGS, SOHO)

Table 1. Potential drivers of effectiveness as identified through CGS data analyses

	Drug B	Drug D	Drug K	Multivariate models
Patient-related variables				
Younger age (<median value)	No	No	No	No
★ Female gender	Yes	Yes	No	Yes/no
★ Tobacco smoking	Yes	No	No	No
Cannabis use	No	No	No	No
★ Poor adherence to previous APD	No	Yes	Yes	
Disease-related variables				
★ Lower lifetime maximal severity of disease	Yes	No	No	Yes
★ Disease stage<5 years	No	No	Yes	No
★ Higher negative symptoms (score≥10)	Yes	Yes	Yes	No

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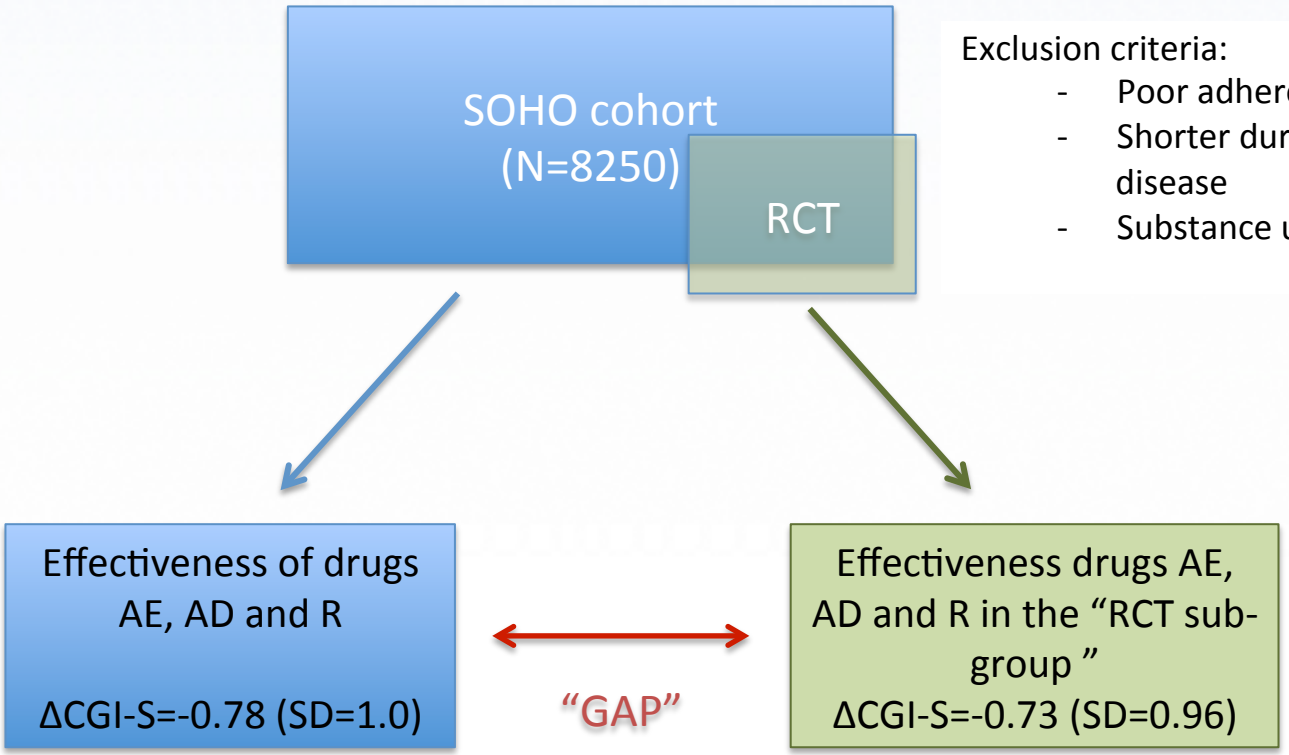
3. Data analyses to identify drivers of effectiveness

On 2 observational datasets in schizophrenia (CGS, SOHO)



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3. Data analyses to identify drivers of effectiveness / conclusions SOHO analyses

Table 2. Measures of the 3-month outcome, in subgroup of patients using the 2 levels of each exclusion criteria

			Symptoms improvement, in patients without the exclusion criteria		Symptoms improvement, in patients with the exclusion criteria		
	N	**Mean ΔCGI-S (SD)**	**n**	**Mean ΔCGI-S (SD)**	**n**	**Mean ΔCGI-S (SD)**	***p*-value**
All drugs	8250	-0.78 (1.0)					
Poor adherence			7930	-0.78 (1.0)	320	-0.89 (1.05)	0.055
Duration of illness ≤ 3 years			5814	-0.73 (0.97)	2436	-0.89 (1.05)	<0.001
Substance use disorder			7855	-0.78 (0.99)	395	-0.80 (1.1)	0.679

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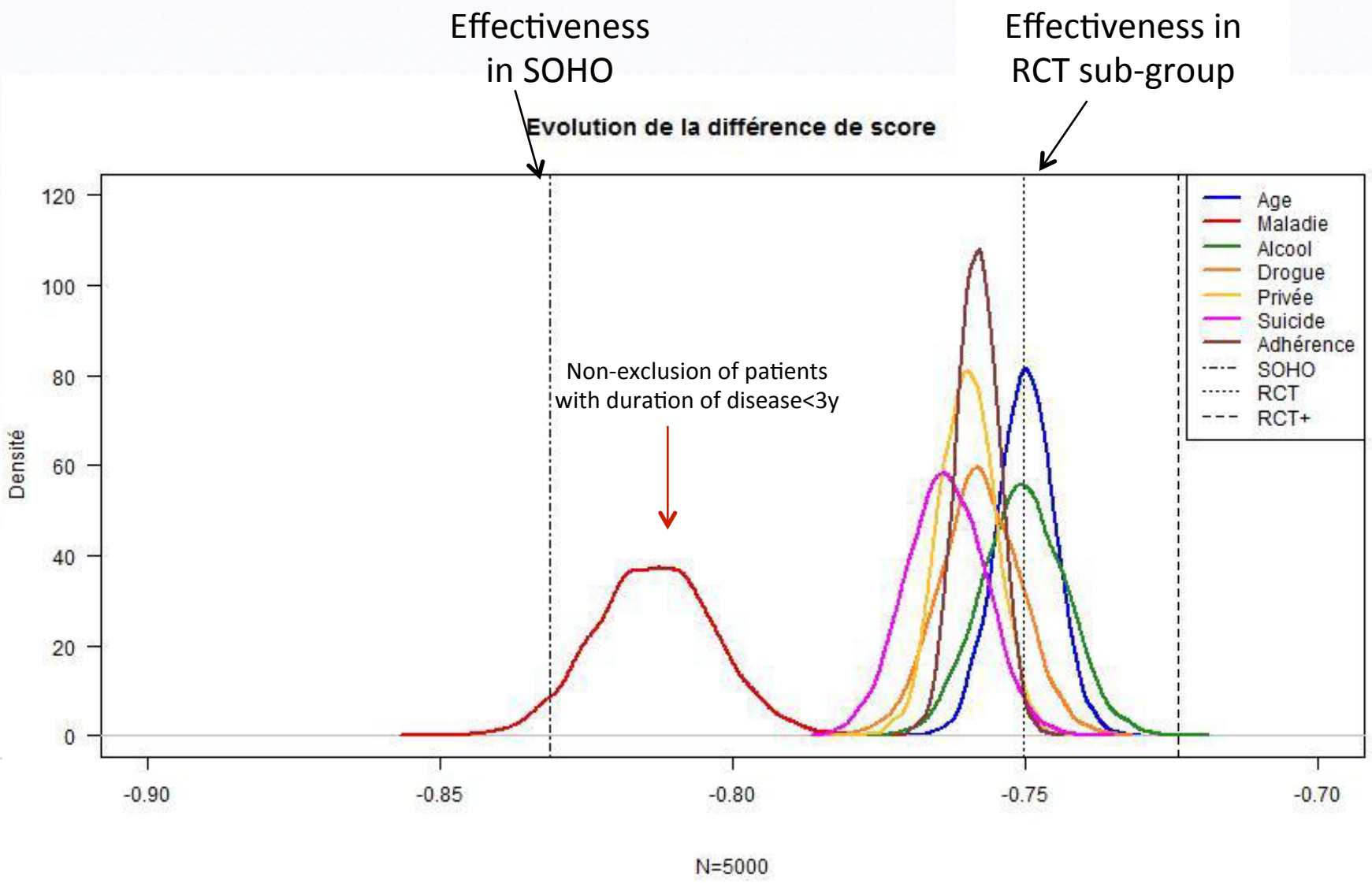
Figure 1. Impact of non-excluding patients, according to each exclusion criteria



Conclusion / identify drivers of effectiveness in schizophrenia

- Disease duration was consistently evidenced as a driver of effectiveness
  - From literature review
  - From experts' interviews
  - In one patient-level data analyses (CGS cohort)
  - In a second patient-level data analyses (SOHO)

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Methods to implement knowledge on drivers of effectiveness

Maximizing trial generalizability

Hélène Karcher, LASER Analytica

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Two ways to improve learning about effectiveness early in clinical development

1. More pragmatic design, i.e., any aspect of study design : population, type of randomization, blinding, monitoring, etc.

2. Better "analyses tools" , i.e., any aspect of data analyses : statistical or model-based analyses, predictive models, etc.

Systematic review of methods to incorporate pragmatism pre-authorization: results*

1. Many (39) methodological papers were identified that recommend how to relax trial features to make them more pragmatic, and to adapt analyses
2. However, this does not translate into many actual Phase 2-3 trials with pragmatic elements – due to scientific and operational hurdles
   - Systematic review only identified 18 pre-authorization trials with pragmatic elements
   - Typically only 1-2 selected features are pragmatic
     - Features required to conduct the trial for authorization
     - Features that could demonstrate a benefit not present in an RCT setting

* Karcher, Nordon, Neumann, Nikodem, Zyla, Chevrou-Severac, Jimenez, Bala, Abenhaim. Methods to Evaluate Real-World Effectiveness in Pre-Authorization Trials SLR. HTAi 2015.

Hurdles to incorporating effectiveness before authorization* (review of 39 articles)

1. Known and unknown confounders in real-world trials may lead to inconclusive effect sizes[18,25]
2. Extensive cost of running such trials due to larger sample size required[14]
3. Operational difficulties in recruiting certain populations, and in minimising measurements/study visits[30,31]
4. Uncertainty in reactions from regulatory bodies[30,32]

* Karcher, Nordon, Neumann, Nikodem, Zyla, Chevrou-Séverac, Jimenez, Bala, Abenhaim. Methods to Evaluate Real-World Effectiveness in Pre-Authorization Trials SLR. HTAi 2015

Generalizability through optimal design - choosing the right population

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37

Real-world study to test eligibility criteria in schizophrenia

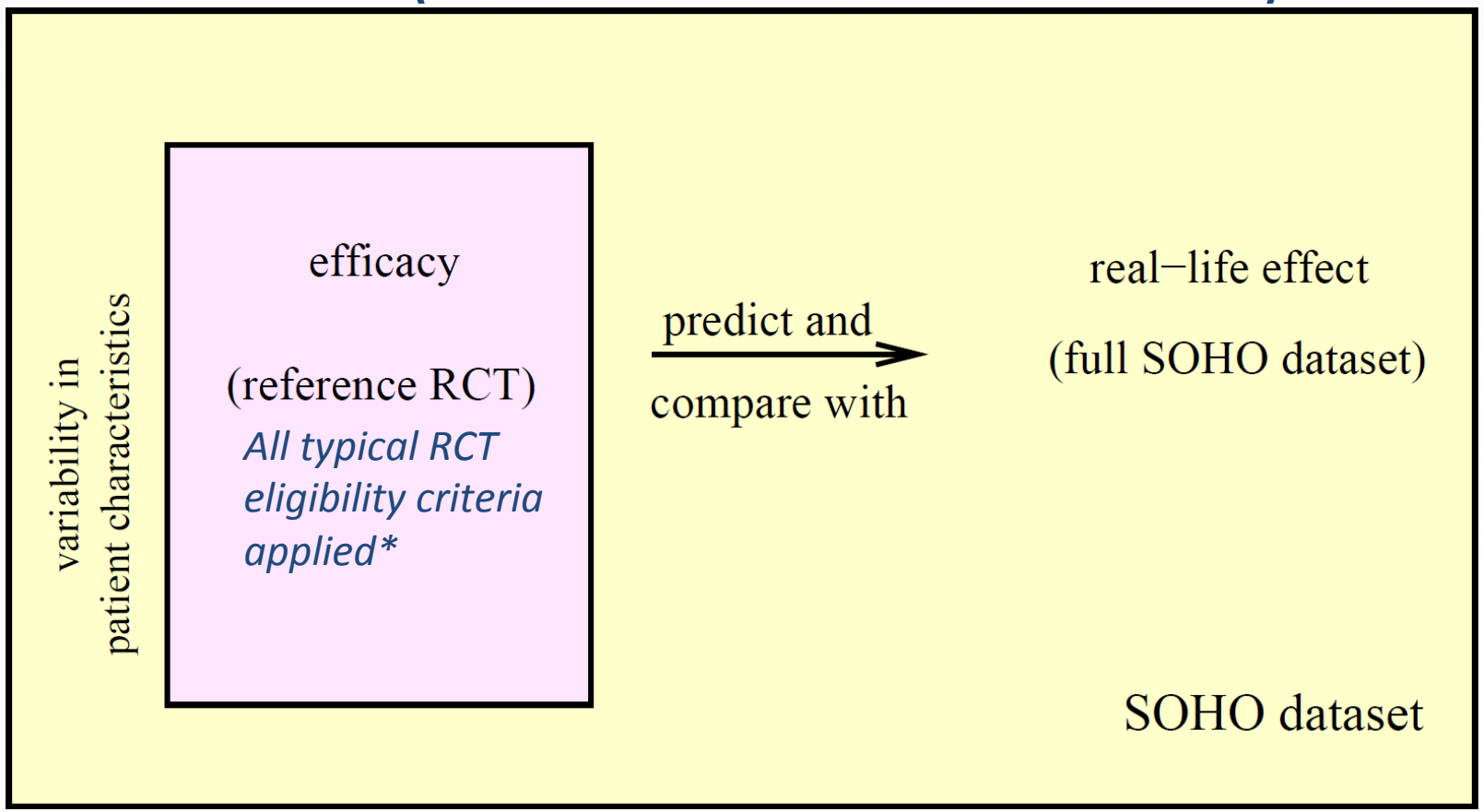
- Objective
  - Explore how to mitigate strict eligibility criteria in Phase 2/3/3b (=RCT, randomized controlled trials) with real-life population heterogeneity

Real-world study to test eligibility criteria in schizophrenia

- Method*: use real-world data to optimize clinical trials
  1. Study patient characteristics and interplay between factors and outcome in a real-life schizophrenia population (SOHO)
  2. Define the subpopulation eligible for a typical pre-authorization trial "reference RCT population"
  3. Re-include in this "reference RCT population" a minimal subset of patients who would usually be excluded (=broaden the eligibility criteria)
     - Method of quotas (stratification) for patient inclusion in trials
     - Combined with predictive modeling of the outcome in the RW population
  4. Evaluate how "efficient" each re-inclusion is

* "Reverse" of the method used in *Schneeweiss et al. Increasing Levels of Restriction in Pharmacoepidemiologic Database Studies of Elderly and Comparison With Randomized Trial Results. Med Care. 2007*

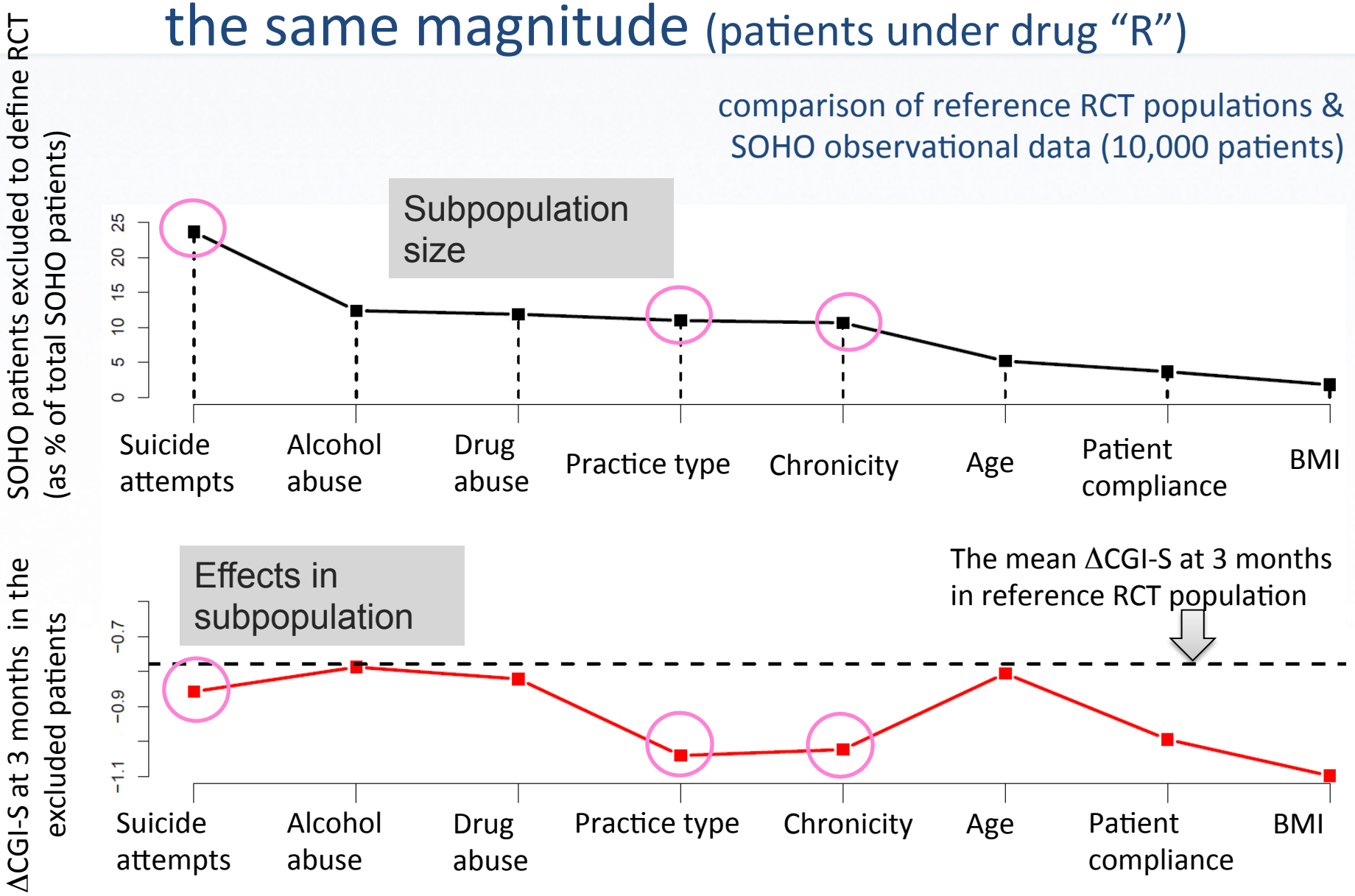
Identify a reference RCT population within SOHO (observational data source)



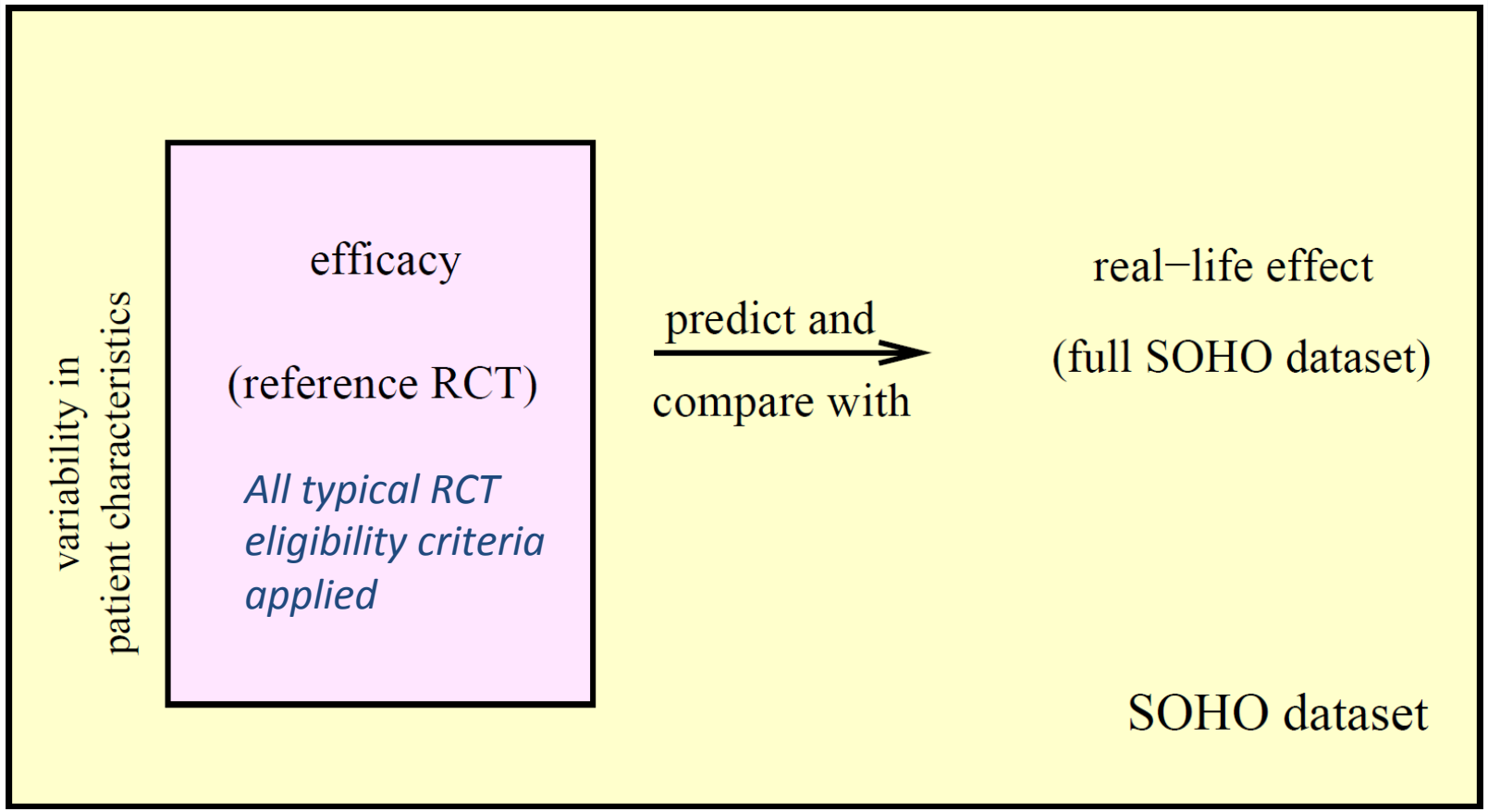
* Leucht et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013

No all exlusion criteria impact effectiveness with the same magnitude (patients under drug "R")

comparison of reference RCT populations & SOHO observational data (10,000 patients)



Use modeling to predict drug effects



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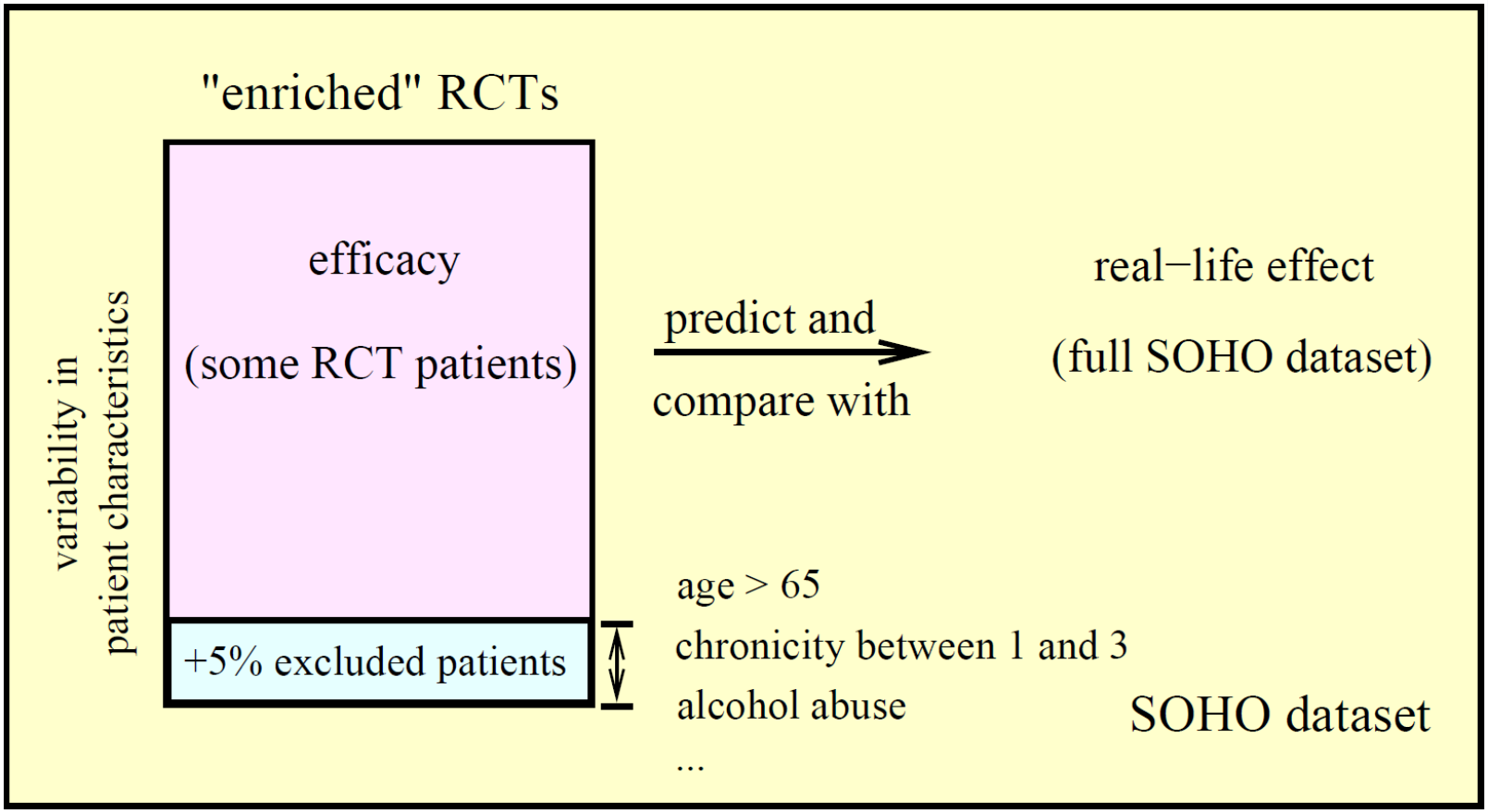
Enriching RCTs to improve predictions



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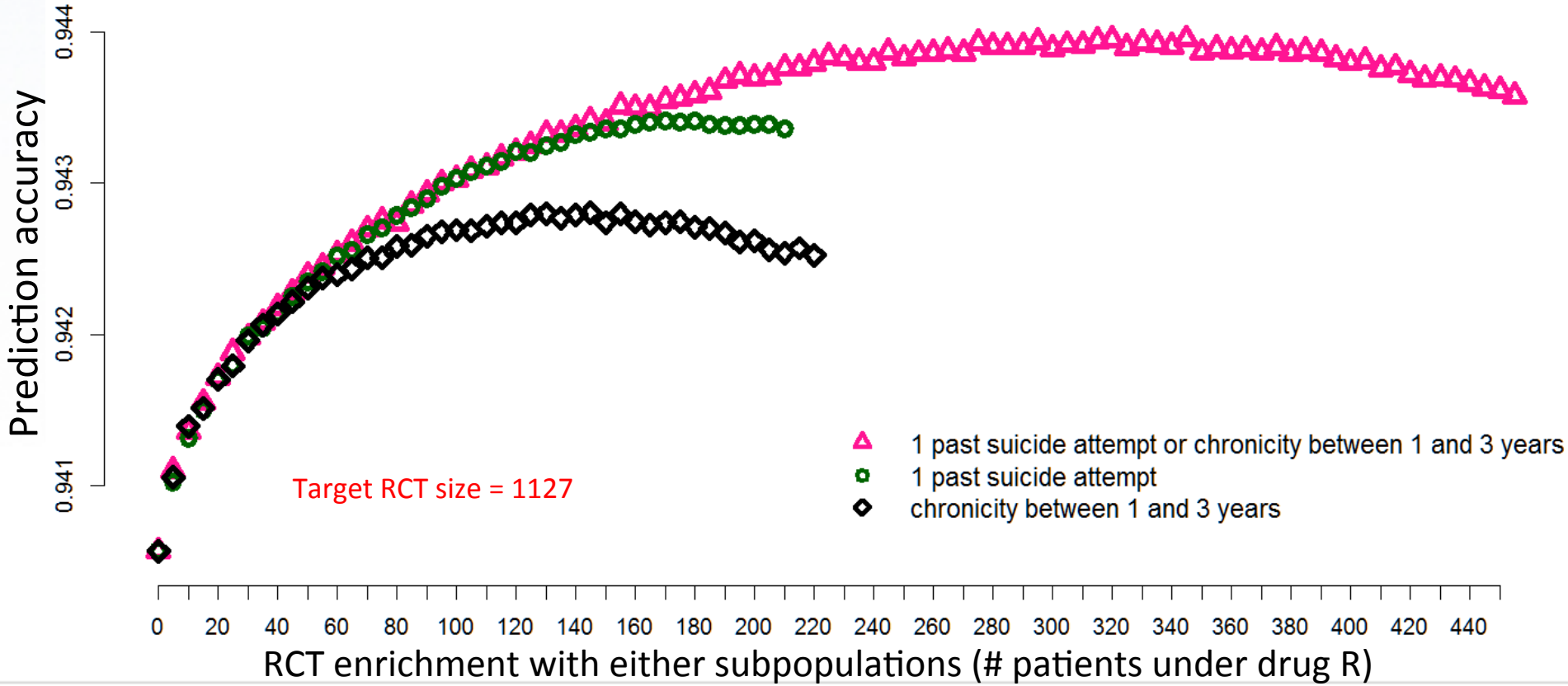
Prediction accuracy from different RCTs enriched in patients with either or both characteristics (simulation results)



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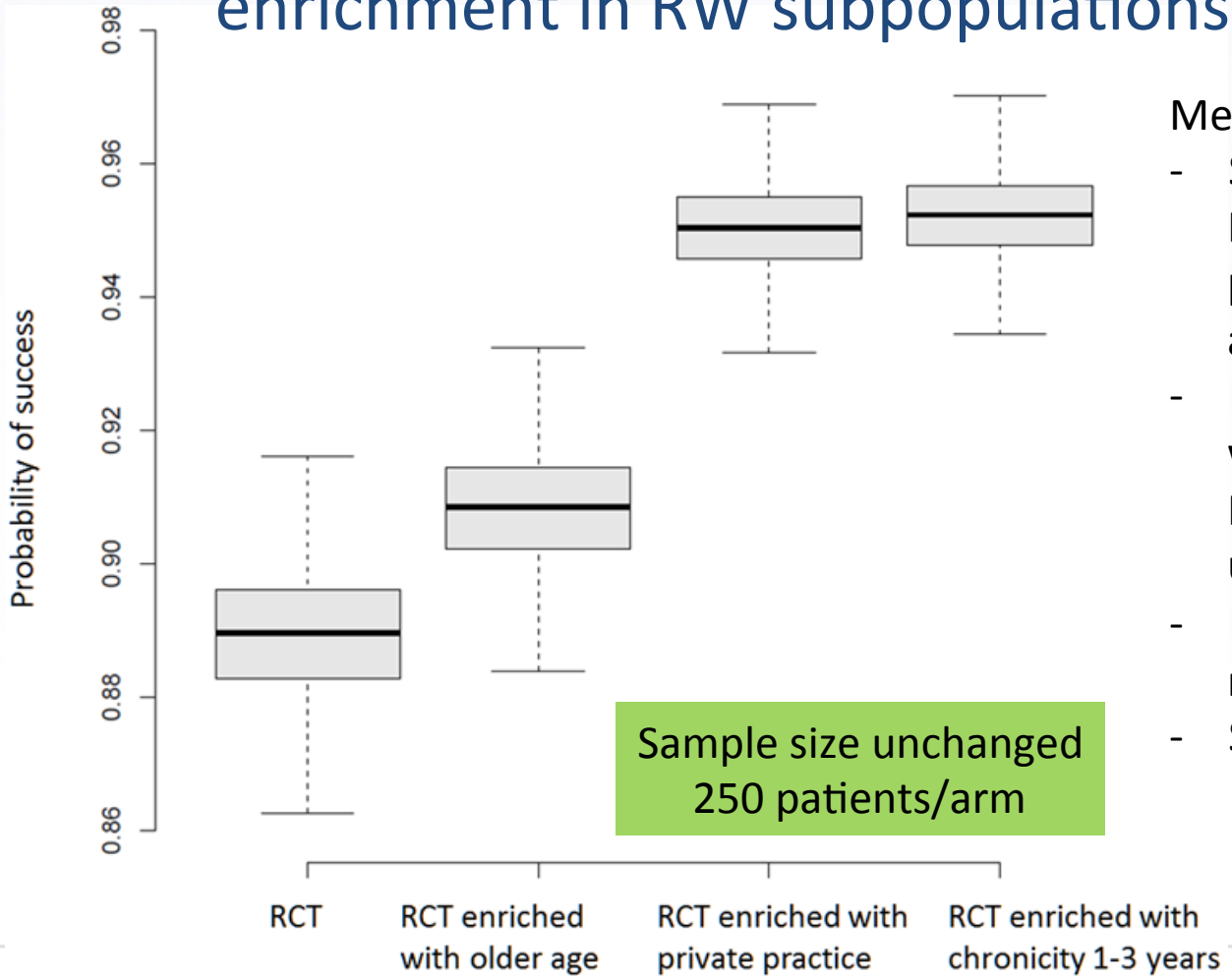
Probability of Success of a parallel RCT increases with enrichment in RW subpopulations



Method:

- Simulate a parallel RCT with 250 patients in each arm (drug R vs AE)
- Random sampling within (enriched) RCT populations under drug R or AE
- Propensity score matching
- Simulate 1000 trials

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Conclusion – methods

- We used a disease registry to guide addition of patient heterogeneity to standard Phase 3 trials in schizophrenia.
- The impact of the following trial design changes was assessed:
  - Relax a few, selected exclusion criteria in a controlled way
  - Quantify the gain in effectiveness prediction accuracy
  - Measure probability of success of the new trial design while keeping sample size

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Conclusion – results

- The best choice of enrichment factor to predict real-life effects was found to be driven by:
  - Size of the excluded real-life population. Excluding "number of past suicide attempts > 1" and "chronicity 1-3 years" left out the greatest schizophrenia population from Phase 3 trials.
  - Change in outcome in patients with this factor. Patients with a practice type "private" and disease chronicity < 5 years had the most different outcome from typical Phase 3 patients.
- Enriching typical Phase 3 with selected factors improved the representability of real-life and as a result, it improved predictions of the real-life effects of the investigated drug.

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Get Real

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Real-Life Data in Drug Development

Towards broader utilization of bridging-to-effectiveness modelling in clinical development

Billy Amzal, LASER Analytica

GetReal WP2 – Live Broadcast

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Questions

1. What drivers of effectiveness to consider?
2. Can you find them in the literature?
3. Can you identify them before launch from existing observational data?
4. Can you take them into account in developing trials?
5. Can you predict/anticipate what the effect will be in real life?

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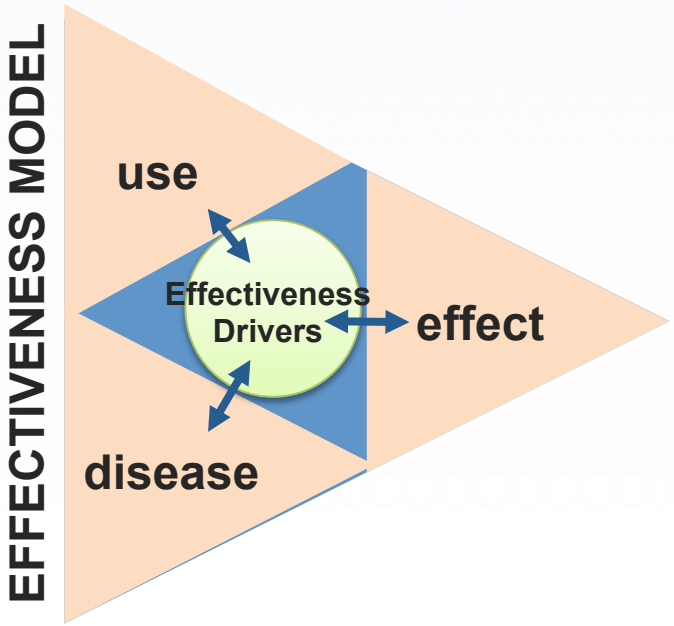
Bridging-to-effectiveness modelling for clinical development

3 interactions or effect modifications to model:

- Use model
- Effect model
- Disease model

Data required on:

- Interactions with DoEs (drug-specific)
- Distributions of DoEs (country specific)



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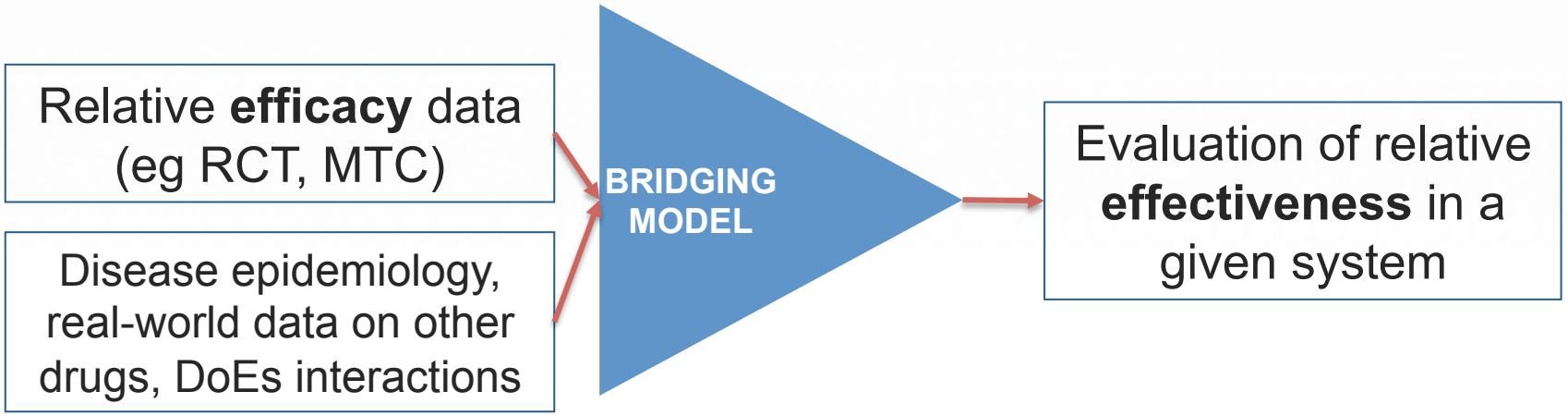
Bridging-to-effectiveness modelling for clinical development

To bridge effectiveness gap, and anticipate extrapolation

- From a selected population to a real-life population
- To other comparators (e.g. with new comparators)
- From short term to long term effectiveness or benefit/risk



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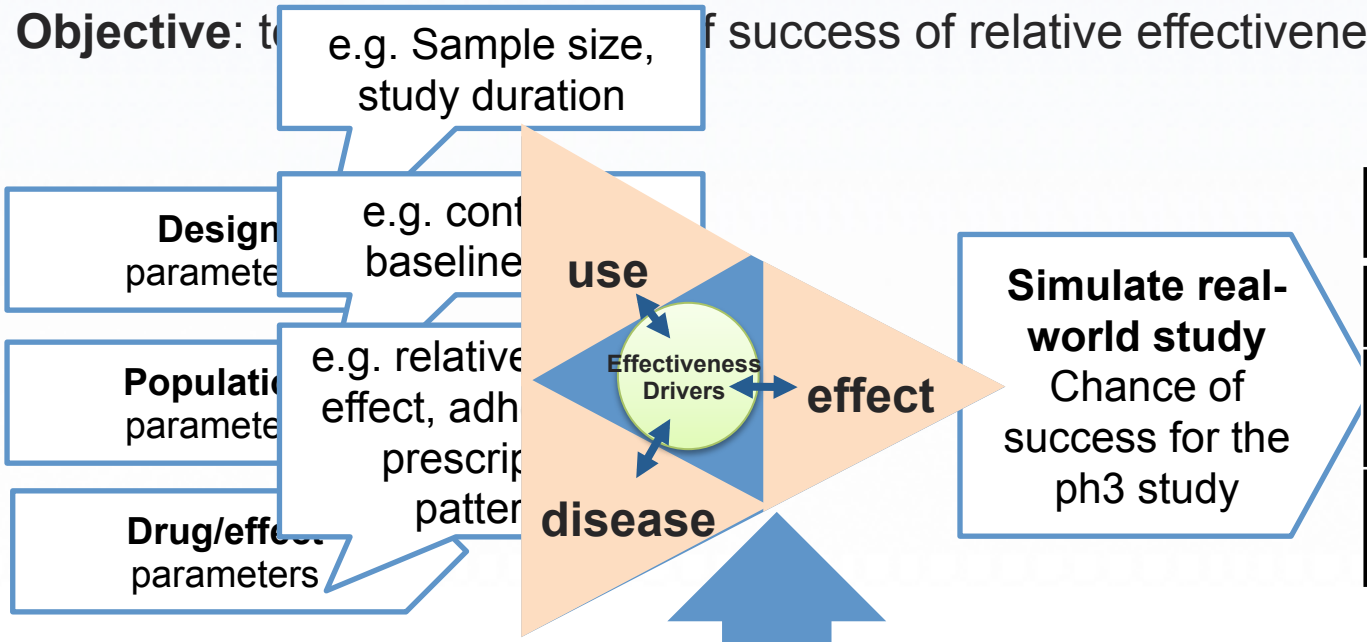
Case study 1: bridging to effectiveness for a new asthma compound to optimize phase 3b study design

Objective: t… f success of relative effectiveness study before launch



Scenarios	6 mo	12 mo	24 mo
Same drug use	5%	4%	5%
X% improved adherence	6%	8%	19%
Y% improved adherence	6%	10%	40%

illustrative

MODEL INPUT
Design parameters

Multivariate inhomogeneous Markov chains informed by observational individual data
Effectiveness drivers: Adherence, severity, treatment sequence

MODEL OUTPUT
chance to get "significant p", given a design

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Real-Life Data in Drug Development

Case study 2: Anticipate relative effectiveness of an oncology drug

- RCTs are typically targeting on selected patients in a well-defined drug positioning and PFS/OS outcomes
- Use of a discrete event model of outcomes with dynamic effectiveness drivers

RW patient	RW physician	Discrete events over time
Drivers of Effectiveness (DoE) • Patients demographics • Prognostic factors • Adherence to treatment • Treatment pattern history	**Precriber characteristics**: • Decision rules to switch • Dose reduction	**Safety outcomes**: • Grade 3 or 4 events **Change in prescription**: • Treatment switch • Dose adjustment • Treatment interruption **Death**

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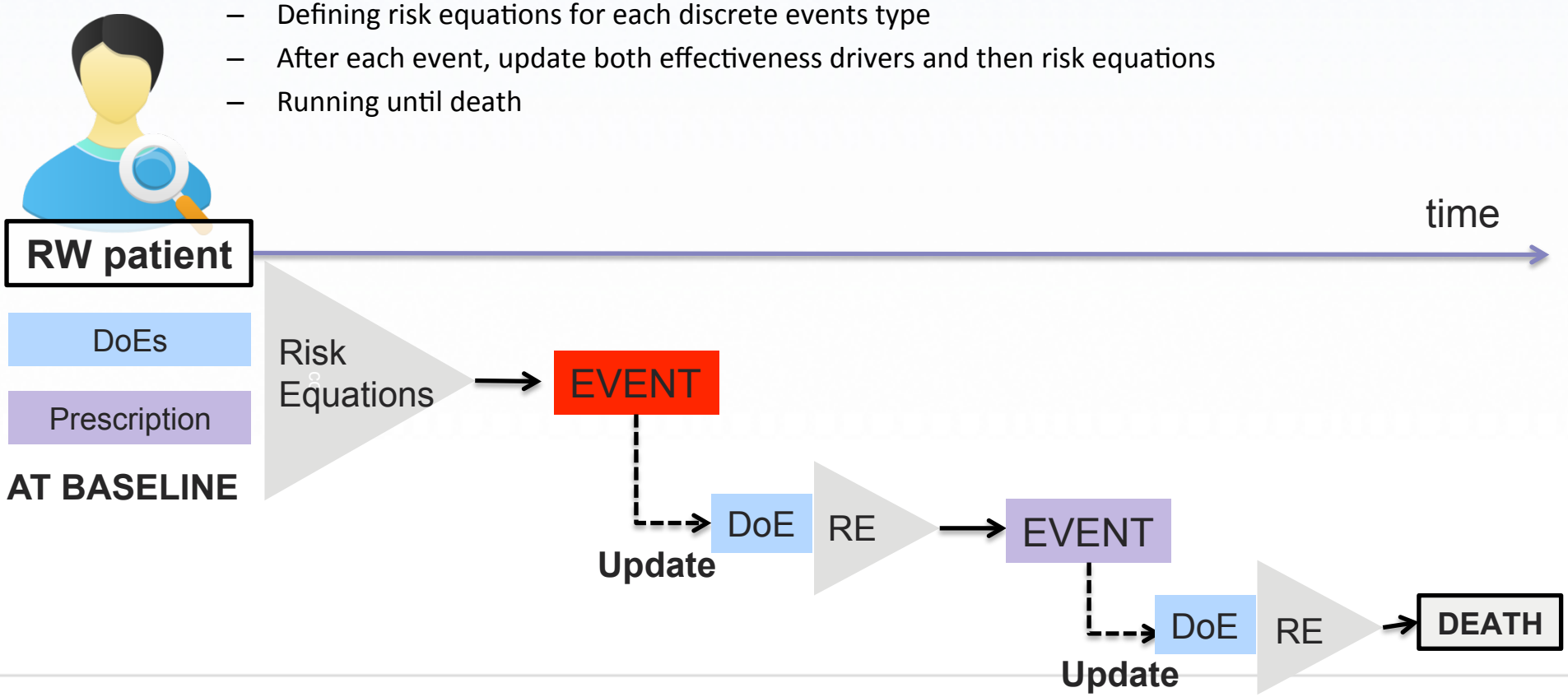
Case study 2: Anticipate relative effectiveness of an oncology drug

- Go beyond RCTs: Simulate patient-level events dynamics
  - Defining risk equations for each discrete events type
  - After each event, update both effectiveness drivers and then risk equations
  - Running until death



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Real-Life Data in Drug Development

Take home messages

- Drivers of effectiveness can be identified early before launch
  - Through literature review and patient-level data analyses
- They can be taken into account in pre-authorization randomized trials, in a controlled manner and without compromising the chance of success
  - Enriched RCT

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Take home messages

- In addition, predictive modeling can help anticipating the effect of the drug in real-life
- Integrative approaches can support bridging real world evidence gaps during clinical development
  - Use of dedicated modelling tools and statistical framework (e.g. Bayesian models)
  - Often requires dynamic modelling
  - Requires some patient-level data
- Support optimal RW study design, positioning and evidence generation planning
  - Including in fast-changing environments (cancer, HIV, HCV), in cases with limited data (orphan diseases, long term outcomes), vaccines
- Fast-growing literature in all therapeutic areas