ECCO2017
EUROPEAN CANCER CONGRESS

27-30 January
Amsterdam,
The Netherlands

Modelling effectiveness from clinical trials

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FROM EVIDENCE TO PRACTICE IN MULTIDISCIPLINARY CANCER CARE

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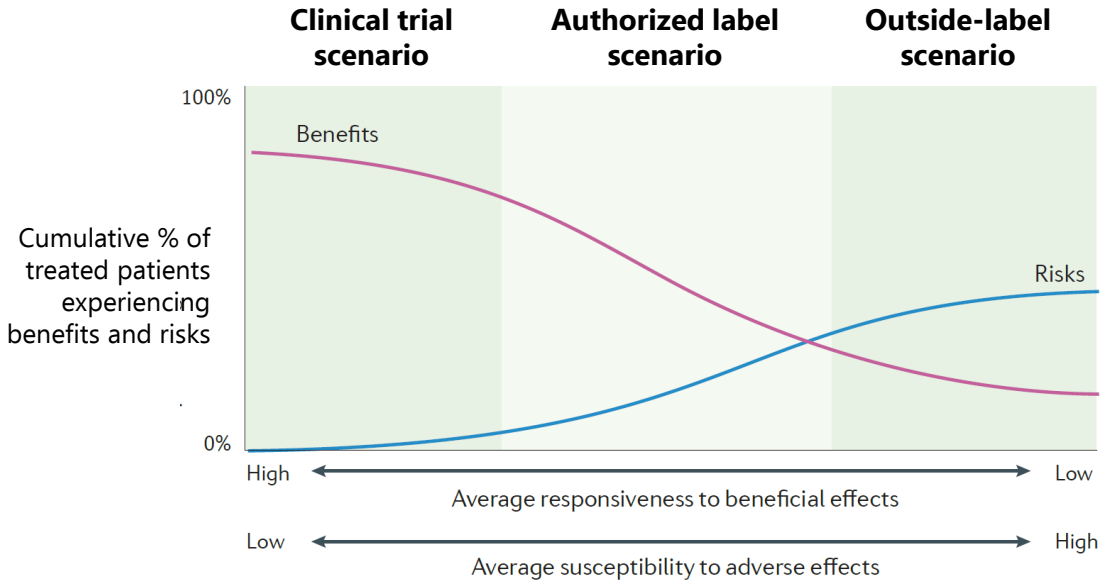
Disclosure

I have no potential conflict of interest to disclose

Clinical trials in despair?

- Failure to achieve patient enrolment targets
- High anticipated costs, poor accrual
- Complex regulatory and monitoring requirements
- Poor representation of routine clinical practice
- Lack of generalizability across different patient populations
- Failure to answer clinically relevant questions



Efficacy-effectiveness gap between data from randomized studies and the real-world evidence

Eichler H-G, et al. Nat Rev Drug Discov. 2011

From efficacy to effectiveness in the real world

Questions	Outcomes	Applicability	Data sources	Synthesis	Conditions
1. How efficacious & safe is this drug?	Efficacy, safety	Typical patients included in clinical trials	(Phase II/III) RCTs	Clinical trials, standard meta-analysis	Study conditions
2. How efficacious & safe is this drug compared to alternatives?	Relative efficacy, relative safety	Typical patients included in clinical trials	(Phase II/III) RCTs	Network meta-analysis	Study conditions
3. How effective & safe is this drug compared to alternatives, in patients who will likely receive it post-launch?	Relative efficacy, relative safety in predicted study populations	Patients predicted to receive the drug post-launch	(Phase II/III) RCTs, clinical databases and registries	Network meta-analysis and meta-regression	Study condictions
4. How effective & safe is this drug compared to alternatives, in patients who will likely receive it post-launch **in the real world of a health care system?**	Relative efficacy, relative safety **in real world populations**	Patients predicted to receive the drug post-launch **in a given health care system**	(Phase II/III) RCTs, clinical databases and registries, **expert opinion, patient preferences**	Mathematical modelling	Real world conditions

(Egger et al, JRSM 2016)

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From efficacy to effectiveness in the real world

7 recommendations

(personal view, based on research findings from IMI GetReal)
www.imi-getreal.eu

Recommendation #1

Do not abandon randomized clinical trials (RCTs)

- Gold standard for generating evidence about relative efficacy
- Relative treatment effects often constant across subgroups
- “Real world” evidence (typically) prone to many issues

Recommendation #2

Allow for mixed treatment comparisons

- Undertake simultaneous inference for all (relevant) treatments
- Provide a ranking of competing interventions

Statistical background: network meta-analysis

Recommendation #3

Perform evidence synthesis, using individual participant data (IPD)

- Generate inferences on *all* relevant evidence
- Account for uncertainty due to missing (outcome) data
- Identify sources of variability in drug response
- Estimate absolute treatment benefits, applicable to individual patients

Recommendation #4

Consider evidence from pragmatic trials and non-randomized studies

- Improve applicability of treatment effect estimates
- Inform disconnected or scarce networks of evidence
- Identify patient populations that will likely receive the drug after launch
- Improve relevance to decision/policy makers and patients

Recommendation #5

Develop predictive models

- Emulate the course of disease
  for an individual or a group of patients under various interventions and conditions
- Adjust for prognostic factors, effect modifiers and heterogeneity
  to facilitate accurate predictions across different populations
- Model the behavior toward drugs' prescription and use
  e.g. treatment preferences, adherence, …

Recommendation #6

Assess generalizability

- Choice of estimands (w.r.t. outcome measure, treatment received, analysis population, time period of interest, treatment adherence status, etc.)
- Presence of conflicting evidence (Statistical heterogeneity or inconsistency)
- Extent of predictive accuracy

Sensitivity analysis, internal, external, and internal-external cross-validation

Recommendation #7

Improve transparency

- Formulation of statistical models & key assumptions
- Reporting standards
- Access to raw data and source code
- Use of (open source) software allowing for reproducible results

The ADDIS software platform

An evidence-based decision support system for health care policy decision making

- Evidence synthesis (Meta-analysis)
- Decision analysis (MCDA)
- Repository of (summary level) trial data
- Web-based user interface
- Open source software packages (R)

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