EFSPI EUROPEAN FEDERATION OF STATISTICIANS IN THE PHARMACEUTICAL INDUSTRY
Representing Statistical Associations in Europe

Evidence Synthesis for HTA

Squaring the Circle: bridging innovation with application

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Indirect treatment comparisons

Is there a gap in the market?

Lytske Bakker, Open Health

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Content

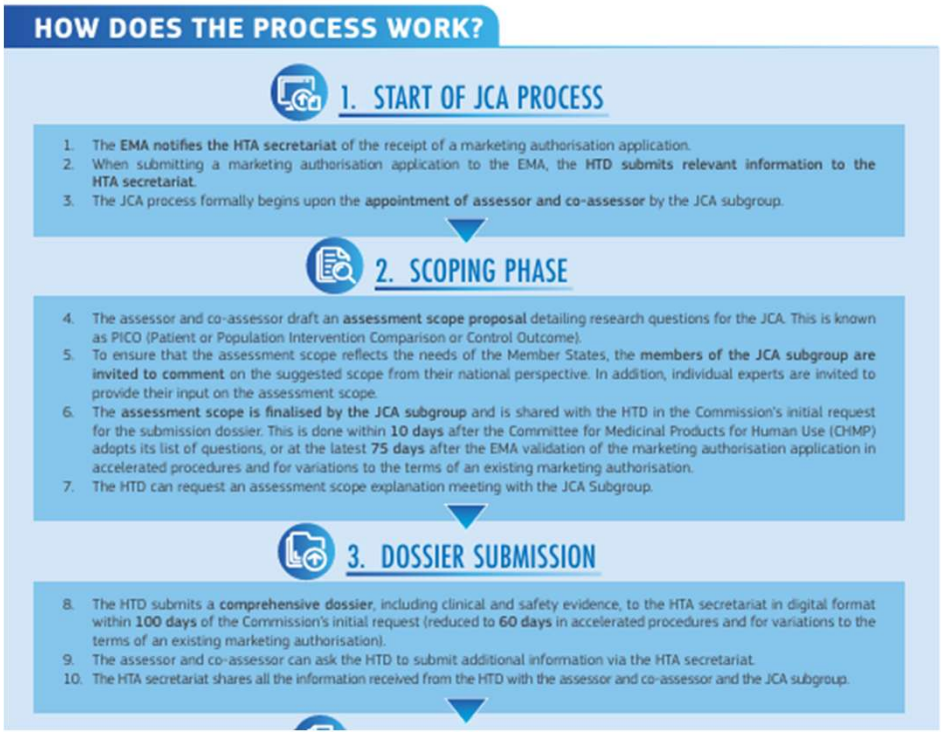
- Indirect Treatment Comparisons- the methods
- Review of indirect treatment comparisons
    - An overview of methods used
    - Criticism of methods adopted
- Introduction of the panel

Acknowledgements

The content of this presentation was developed together with Bodille Blomaard, Svenja Petersohn and Claire Ainsworth

Background

- The Joint Clinical Assessment (JCA) gives companies 100 days to submit a *comprehensive* dossier
- Many Patient, Intervention, Comparator, Outcome (PICOs) combinations?
  - Many indirect treatment comparisons (ITC) in 100 days
- Swift adoption and use of best practice methods is essential to meet with JCA requirements



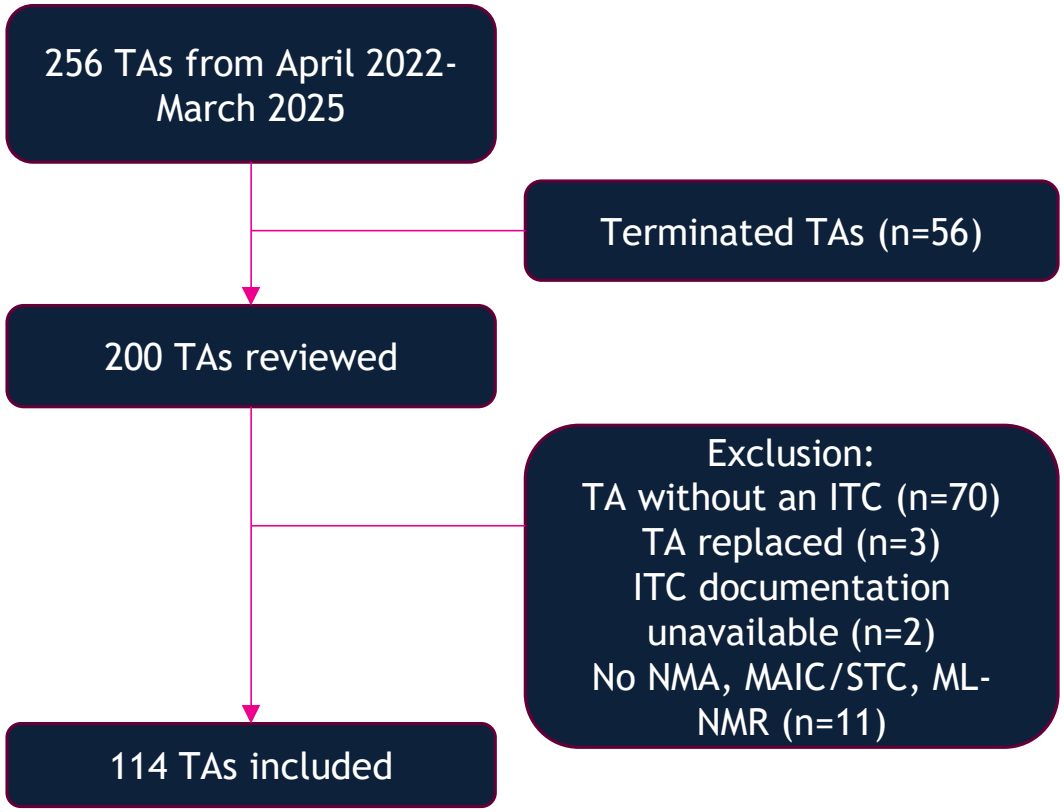
ITCs – methods

	NMA	MAIC	STC	ML-NMR
Comparison	Multiple (n ≥ 2) treatment effects	Single comparison	Single comparison	Multiple (n ≥ 2) treatment effects
Data needs	Aggregate only	IPD (1 study)	IPD (1 study)	IPD (≥1 study)
Treatment effect can be estimated for	Assumed population of included studies	Population of aggregate data	Population of aggregate data	All trial populations included in the analysis, **and** within populations where treatments have not been observed*
Adjustment for population differences to reduce bias in estimates	✓	✓	✓	✓
Feasible with single-arm trials	✗	✓	✓	✗
Can be performed without a common comparator arm	✗	✓	✓	✗
Acceptability	"Gold standard"	Most frequently used PA-ITC	Recommended for unanchored ITC	Newest methodology, growing traction

* Providing relevant covariate information for that population is available

ITC methodologies- the status quo

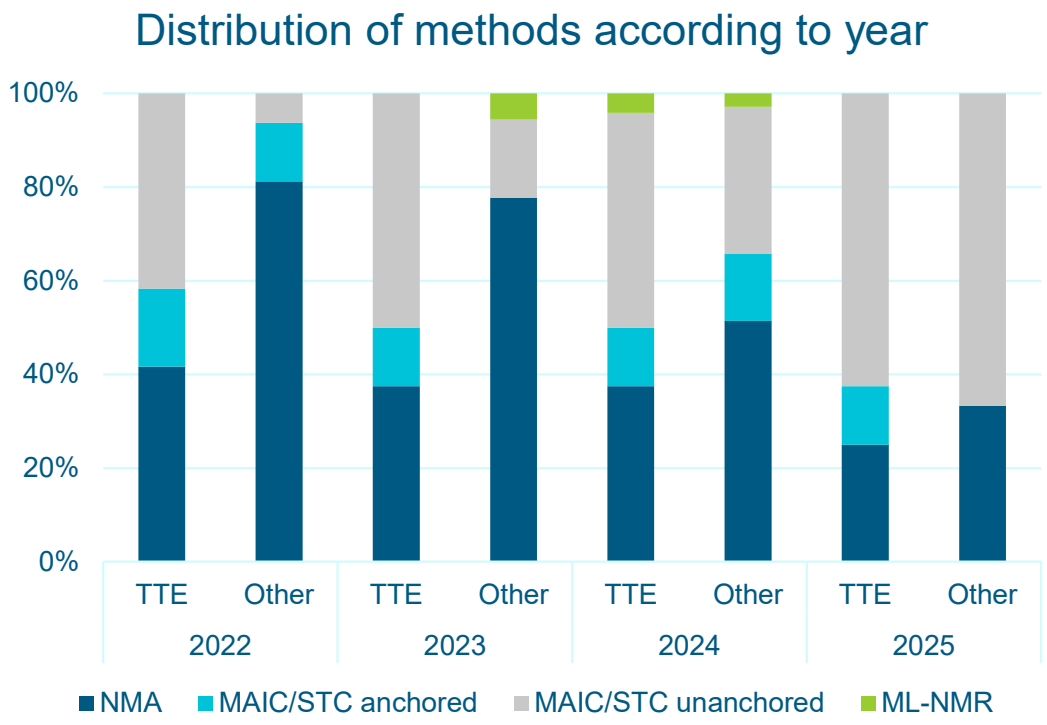
- Identify methods adopted and criticism expressed by the National Institute for Health and Care Excellence (NICE)
- Submissions from April 2022-March 2025
- Exclusion criteria:
  - Termination of the appraisal
  - No ITC performed
- Including NMAs/MAICs/STCs/ ML-NMRs



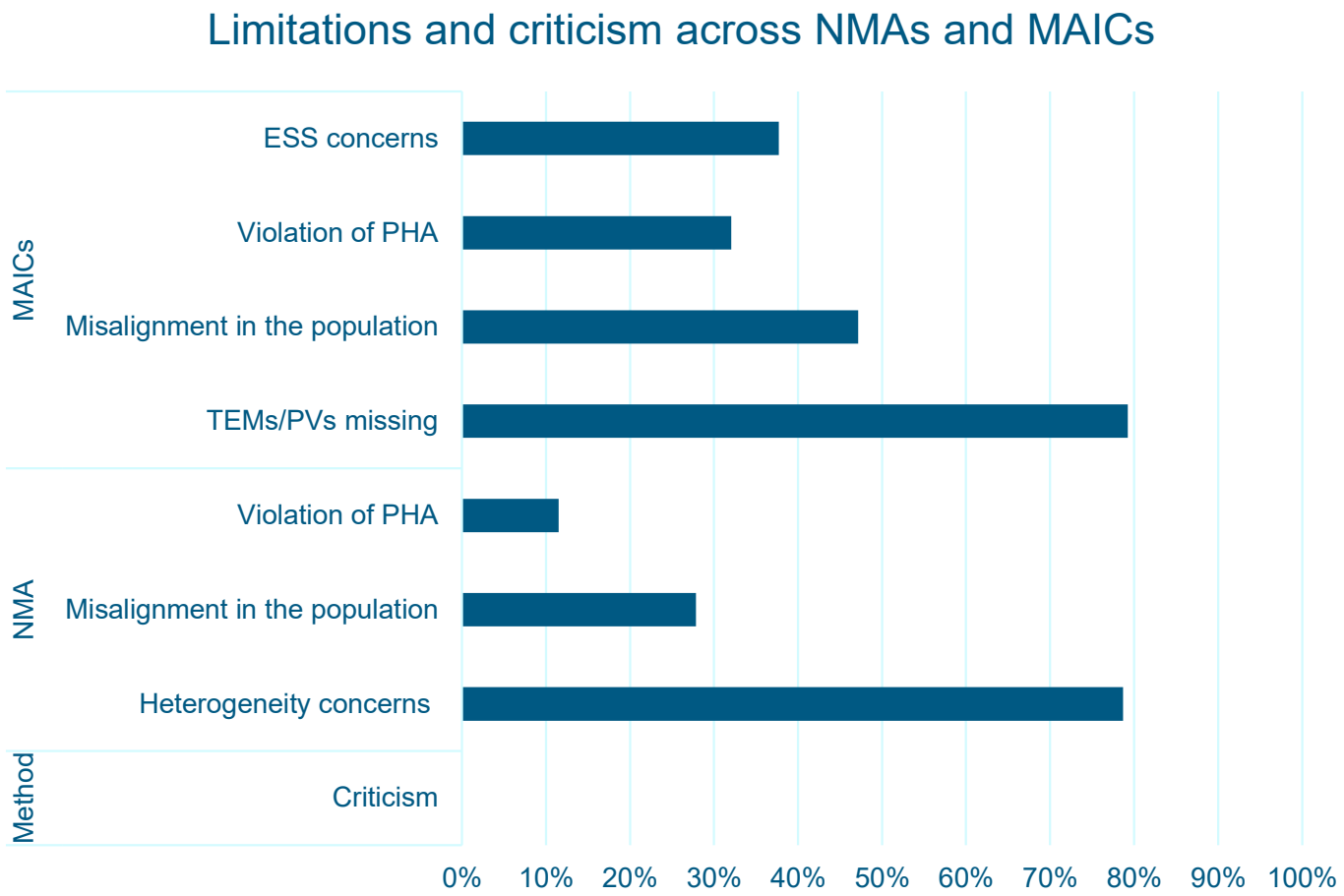
ITCs- Current practice

- NMAs were most often used followed by unanchored MAICs
- STCs were rarely used
- ML-NMRs were only recently available and thus seen less often

- The outcomes reported were most often binary (n=56) or time-to-event (TTE) data (n=60)



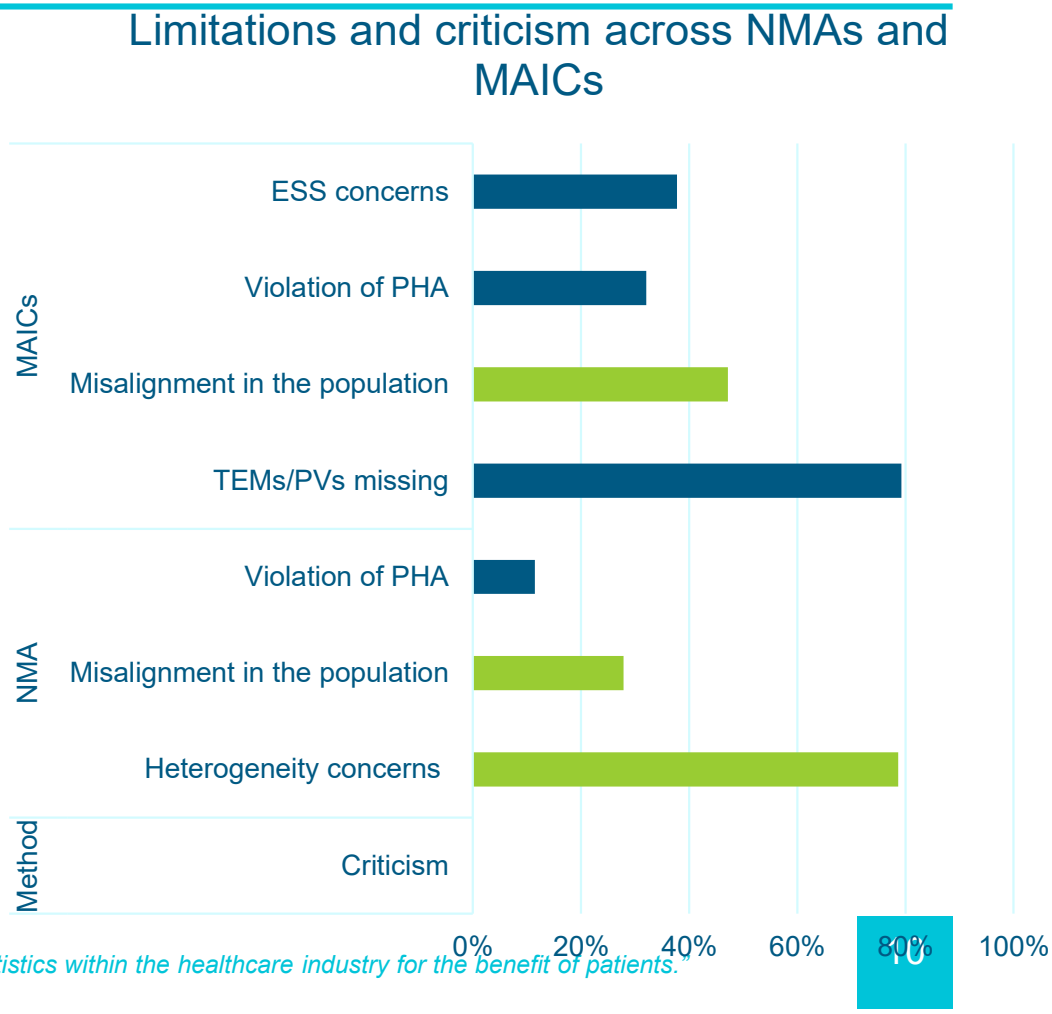
ITCs- Criticism and challenges



ML-NMR: A need for better methods?

- NMAs and MAICs most often used
- Challenges identified:
  - Misalignment between populations (47% MAICs and 28% NMAs)
  - Both MAICs and NMAs in 13% of TAs
  - Heterogeneity in NMAs in 79% of TAs

- **Nicky Welton** will introduce ML-NMRs as a method and discuss the underlying assumptions



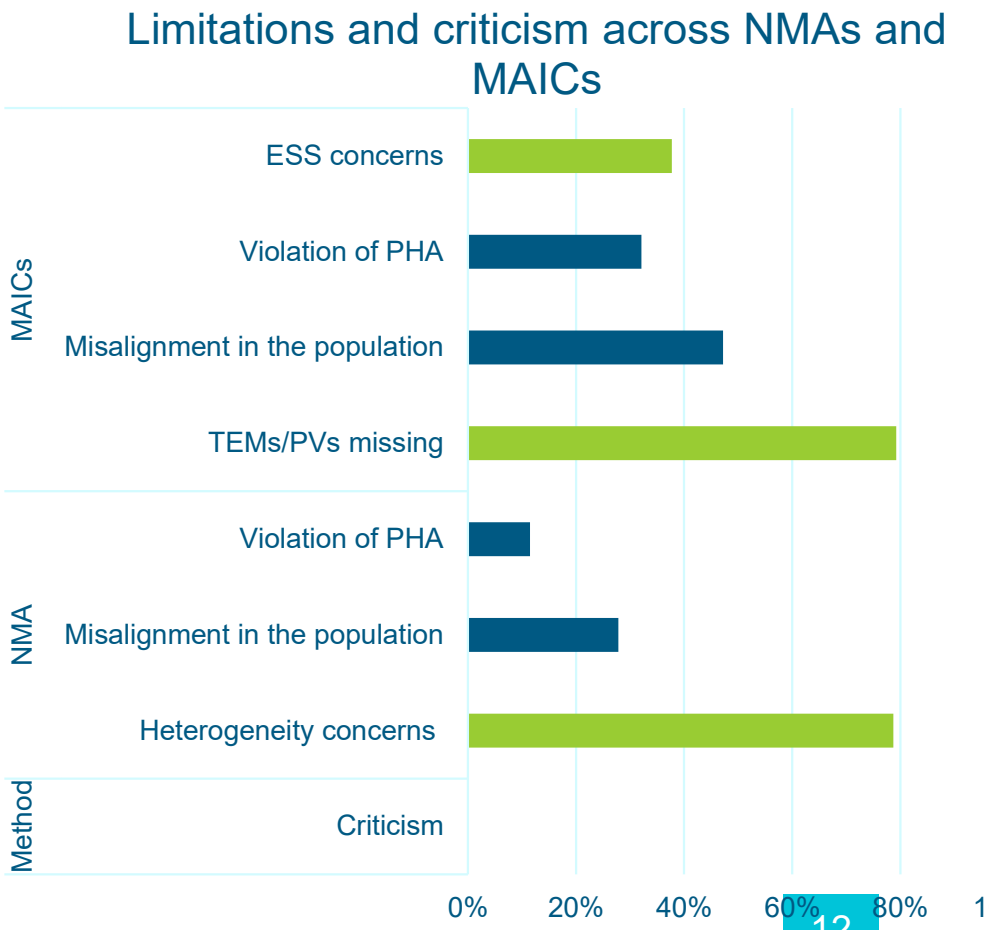
ML-NMR: How to ensure adoption?

- ML-NMRs coincide with an increased layer of complexity
  - STC's (n= 6) are rarely used despite recommendations[1,2]
  - Companies seem to avoid random effects in 23% of submissions
  - Proportional hazard assumption is often criticized (32% of MAICs)

- **Min-Hua Jen** will discuss challenges when considering the use of ML-NMR from an industry perspective

Better methods? Better planning!

- Misalignment between planning of trials and evidence required for HTA dossiers?
  - Missing treatment effect modifiers and prognostic variables in 79% of MAICs
  - Effective sample size concerns in 38% MAICs
  - 74% of MAICs is unanchored
- **Gregory Chen and Anders Gorst-Rasmussen** will discuss quantitative scenario planning for ITCs



Better methods *or* better planning

- Efficiency is key
  - JCA requires companies submit their dossier within 100 days after receiving their PICO's
  - Not *another* sensitivity analysis; 33% of ITCs presented multiple methods

- Advance HTA decision-making
- **Keith Abrams** will conclude with a discussion on how novel methods and better planning can result in better evidence dossiers

Speakers and topics

- **Nicky Welton-** Multilevel network meta-regression- the method
- **Min-Hua Jen-** Multilevel network meta-regression- the new golden standard for industry?
- **Gregory Chen and Anders Gorst-Rasmussen-** Adaptive integration and software engineering to drive planning and execution of ITCs for EU HTA- The early bird gets the worm
- **Keith Abrams-** Better methods or better planning? - Improving HTA decision-making
- Panel discussion

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Multilevel network meta-regression

The method

Nicky Welton, University of Bristol

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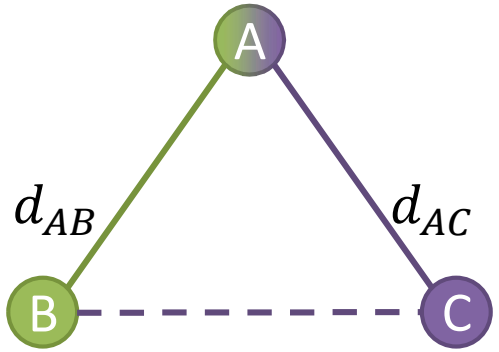
Indirect Comparisons: Assumption

- Assumes constancy of relative effects:
  - $d_{AB(AB)} = d_{AB(AC)}$
- Biased if there are imbalances in effect modifiers between AB and AC
  - $d_{AB(AB)} \neq d_{AB(AC)}$
- "Anchored" indirect comparisons are robust to differences in purely prognostic factors between trials
  - due to randomisation

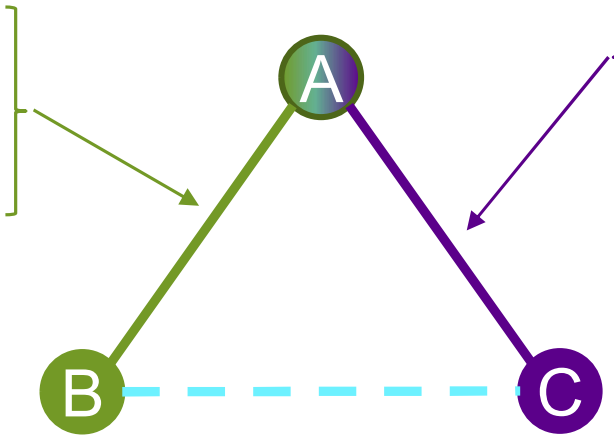


Population Adjusted Indirect Comparisons

- Seek to adjust for imbalance in effect modifiers (EM)s
- Create a fair comparison in a specific target population
  - ie for a given set of EMs
- Common scenario: limited IPD

AB trial: IPD

Y_i	T_i	X_{1i}	X_{2i}	...



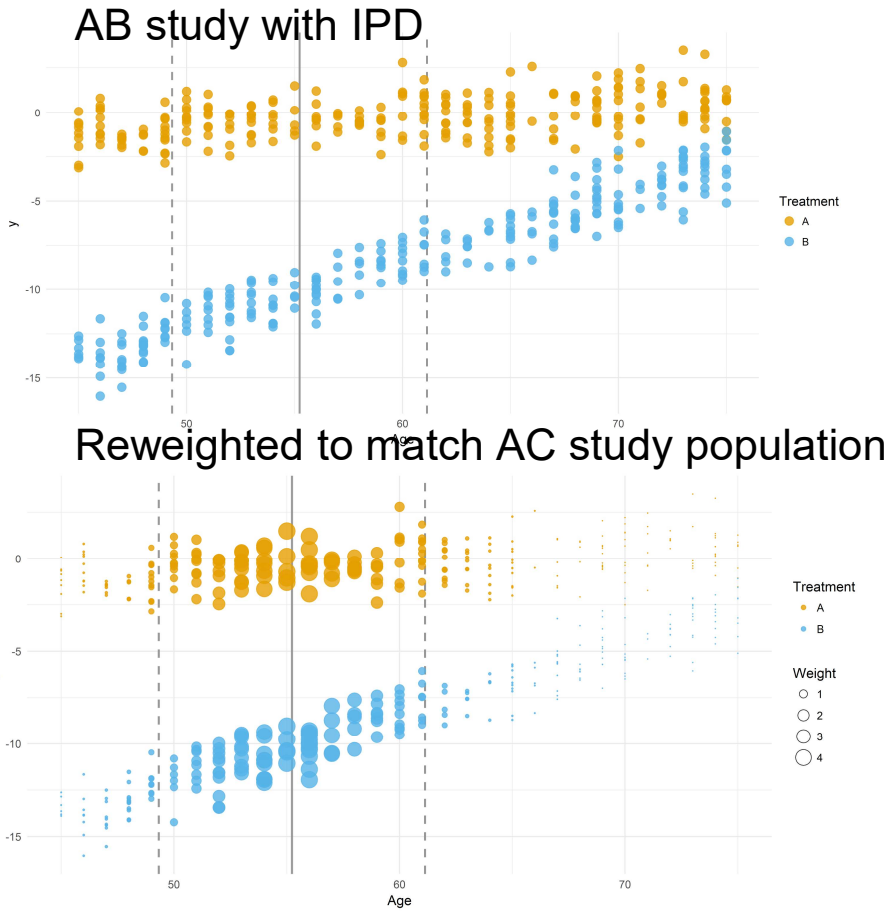
AC trial: aggregate data for outcomes and covariates

$\bar{Y}_A, \bar{Y}_C, \bar{X}_1, \bar{X}_2, \ldots$

$\sigma_A, \sigma_C, f_X(\cdot)$

Matching-Adjusted Indirect Comparison (MAIC) Signorovitch et al. (Pharmacoeconomics 2010)

- Population reweighting method
  - similar to propensity score weighting
- Effective sample size depends on overlap between studies
  - can give unstable / imprecise estimates
- Frequently used in NICE TAs



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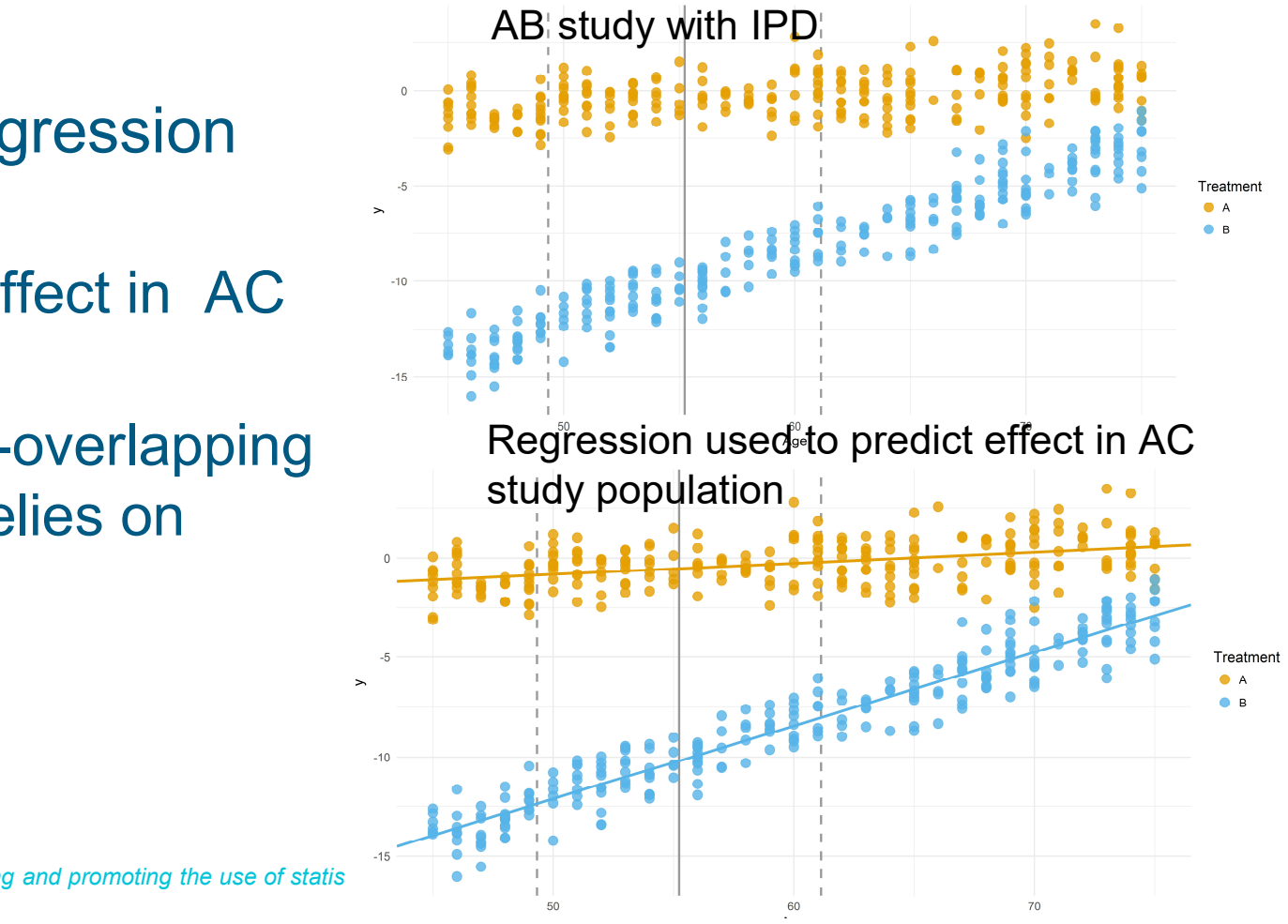
Simulated Treatment Comparison (STC) Ishak et al. (Pharmacoeconomics 2015)

- Create an outcome regression model in the AB trial
  - predict AB relative effect in AC population
  - can be used for non-overlapping populations … but relies on extrapolations …



Limitations of MAIC and STC

- Both produce estimates of relative treatment effect that are specific to the AC population
  - May not represent the target population for the decision
- MAIC performs best when sufficient overlap in trial pops
  - … but then population adjustment isn't needed!
- Neither generalise to larger networks
  - Performing several MAICs/STCs from one IPD study into several aggregate studies is invalid
    - Mixing different populations, different adjustments, multiple uses of the same data etc.

Multilevel Network Meta-Regression (ML-NMR) Phillippo et al (JRSSA 2020)

- Define an individual-level regression model

individual i, study j, treatment k

Individual:

$$y_{ijk} \sim \pi_{\text{Ind}}(\theta_{ijk})$$

"link" eg logit

$$g(\theta_{ijk}) = \eta_{jk}(\boldsymbol{x}_{ijk}) = \mu_j + \boldsymbol{x}_{ijk}^{\mathsf{T}}(\boldsymbol{\beta}_1 + \boldsymbol{\beta}_{2,k}) + \gamma_k$$

covariates; covariate main effect; covariate x treatment interaction; treatment main effect

- Aggregate-level model obtained by integration (Quasi MC)

Aggregate:

$$y_{\bullet jk} \sim \pi_{\text{Agg}}(\theta_{\bullet jk})$$

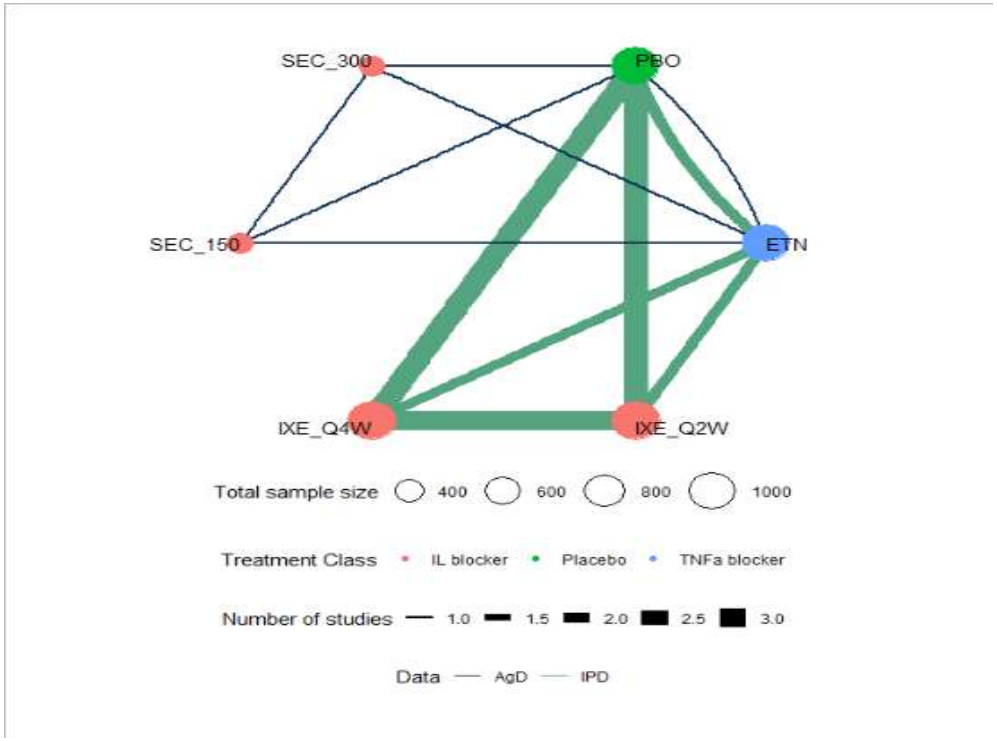
$$\theta_{\bullet jk} = \int_{\mathfrak{x}} g^{-1}\left(\eta_{jk}(\boldsymbol{x})\right) f_{jk}(\boldsymbol{x})\, d\boldsymbol{x}$$

covariate distribution

  - Use copula for covariate distribution, and Quasi MC integration

Multilevel Network Meta-Regression (ML-NMR)

- General framework with special cases:
  - IPD network meta-regression with full IPD
  - Standard NMA with no adjustment
- Can be used in networks of all sizes
- Implemented in `multinma` R package



Relative Effects in Target Decision Population Phillippo et al (MDM 2023)

- Integrate relative effects over covariate distribution to obtain relative effects in target population

$$\int_{X} \left(x^T \beta_{2,k} + \gamma_k \right) f(x) dx$$

- The target population could be represented by
  - A registry data set
  - An observational study
  - An RCT

ML-NMR: Identifiability

- Independent EM interactions
  - Requires IPD, or several Aggregate data studies at different covariate values, on each treatment
- Exchangeable EM interactions
  - Similar data requirements to independent EM interactions, plus multiple treatments needed to estimate shared variance term
- Common/shared EM interactions
  - May be justified for treatment classes

ML-NMR Assumptions

- No unobserved effect modifiers (EMs)
  - Assumed by all population adjustment methods
- Shared EM assumption
  - for identifiability in small networks
  - MAIC and STC also assume this for AC estimates to generalise to other populations
- Form of joint covariate distribution in the AgD
  - Same marginal form and correlation structure as IPD
- Valid to extrapolate outside range of IPD
  - also assumed by STC (MAIC cannot extrapolate)

ML-NMR: Recent Developments

- ML-NMR has been developed for time-to-event outcomes
  - proportional and non-proportional hazards models
  - parametric and flexible (M-spline) survival models
  - implemented in latest version of `multinma`
  - https://arxiv.org/abs/2401.12640
- A beta-version of `multinma` allows the user to enter summary regression coefficients when IPD is not available
- Using ML-NMR with disconnected networks and single arm trials (unanchored indirect comparisons)
  - Work-in-progress (Perren ISCB abstract 2024)

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Multilevel Network Meta-Regression (ML-NMR)

The New Golden Standard for Industry?

Min-Hua Jen, Manoj Khanal, Michael David Sonksen, Eli Lilly

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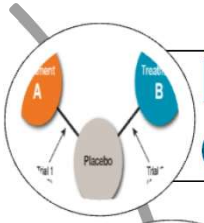
Disclaimer

The content presented is intended for informational purposes only and reflects the views of the presenter based on available data and research

Outline

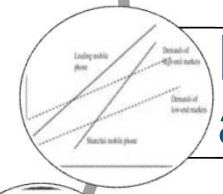
- Growing Use of ML-NMR in Industry
- Challenges in Specifying Treatment Interaction Effects in RCTs and ML-NMR
- Implementation Challenge in Practice
- ML-NMR application in time to event endpoints
- Final thoughts

Growing Use of ML-NMR in Industry

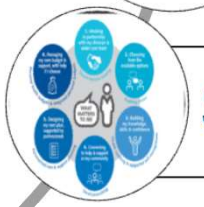


Increasingly applied in population-adjusted indirect treatment comparisons (ITCs)

Especially valuable in large networks with multiple comparators



Enables adjustment for effect modifiers and prognostic factors across studies



Supports personalized and population-level decision making

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Challenges in Specifying Treatment Interaction Effects in RCTs and ML-NMR

- Difficulty Identifying Treatment Interactions (Harrell, 2020*)
  - RCTs powered for average effects, not interactions
  - Even balanced covariates → interaction effects 4× less precise
  - Power effectively 16× lower for differential effects (Gelman)
  - Multiple testing risks false positives
  - Requires a clear, pre-specified rationale

- Subgroup Analysis Limitations
  - Does not prove heterogeneity of treatment effect
  - Often yields unreliable estimates

Harrell 2020 https://www.fharrell.com/post/varyor/#difficulty-of-the-task

Challenges in Specifying Treatment Interaction Effects in RCTs and ML-NMR

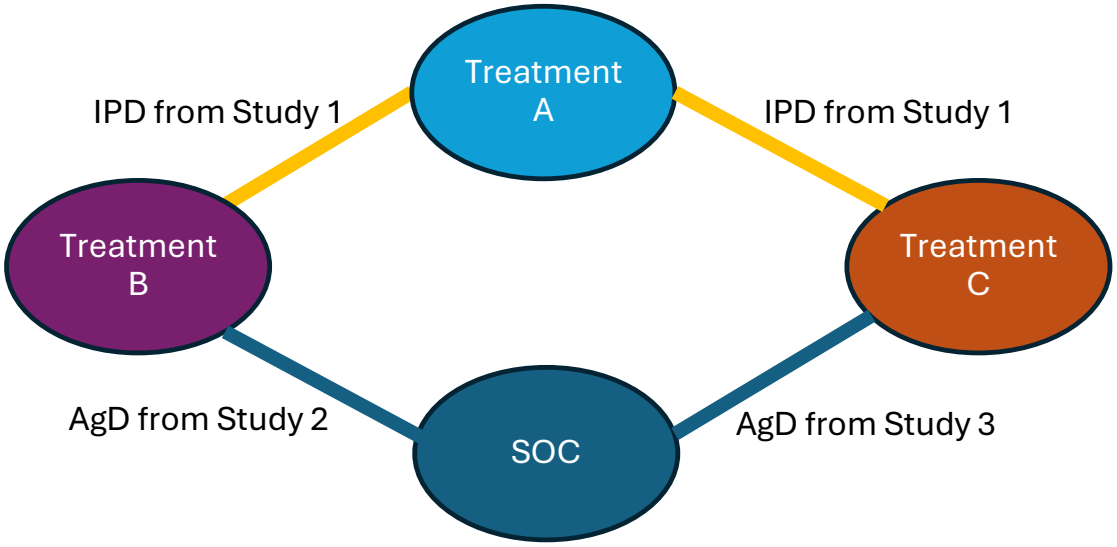
- ML-NMR Assumptions (1 RCT IPD)
  - Interaction is real (not data-mined)
  - Shared effect modifiers
  - Ideally need individual patient data (IPD) from each treatment class

- Implications
  - May limit ML-NMR use vs. standard NMA
  - Still useful as sensitivity analysis

Implementation Challenge in Practice

- Requires advanced statistical expertise in Bayesian hierarchical modelling
- Limited transparency due to proprietary IPD use
- High computational burden and convergence issues
- Performance hinges on covariate selection and model specification

ML-NMR application in time to event endpoints



ML-NMR Model	Random or Fixed	DIC
Piecewise exponential	random	2899.77
Log-logistic	random	2901.47
Log-logistic	fixed	2903.09
Piecewise exponential	fixed	2907.88
Gamma	fixed	2908.77
Mspline with 2 degrees	random	2910.7
Log-normal	random	2911.63
Log-normal	fixed	2911.66
Mspline with 3 degrees	random	2911.93
Weibull	random	2912.22
Mspline with 2 degrees	fixed	2919.29
Mspline with 3 degrees	fixed	2919.65
Weibull	fixed	2920.65
Mspline with 1 degree	random	2925.23
Gompertz	random	2933.67
Mspline with 1 degree	fixed	2934.48
Gompertz	fixed	2941.26
Exponential	random	2971.49
Exponential	fixed	2973.47

Challenges in Applied Settings

- Trade-offs between model performance and computation speed
  - Higher number of integration points means better fit but much slower speed
- Algorithms can be slow even with small networks
  - We experienced 8+ hours for 300k samples in a 3-study network
  - Running all combinations of Fixed/Random effects, different covariates and different likelihoods leads to more computationally intensive tasks
- High memory usage
  - Even in simple networks, posterior samples and predictions may use 80+ GB
  - This becomes even more challenging when using a computing cluster
- Convergence
  - Some models may never converge or require advanced knowledge in stan

Final thoughts

- **ML-NMR is not yet the golden standard**, but a **strong candidate** for HTA-relevant comparisons
- Requires:
  - Data availability
  - Technical capacity
  - Cross-functional collaboration
- Statisticians play a central role in making it accessible and acceptable to HTA bodies
- Balance innovation with transparency and interpretability

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Early integration and software engineering to drive planning and execution of ITCs for EU HTA

The early bird gets the worm

Gregory Chen, MSD Switzerland
Anders Gorst-Rasmussen, Novo Nordisk A/S

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Disclaimer

- Viewpoints are our own and not necessarily those of our companies
- All illustrations are AI-generated

Getting the foundation right

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What if we don’t get the foundation right?

1. Mismatched Evidence

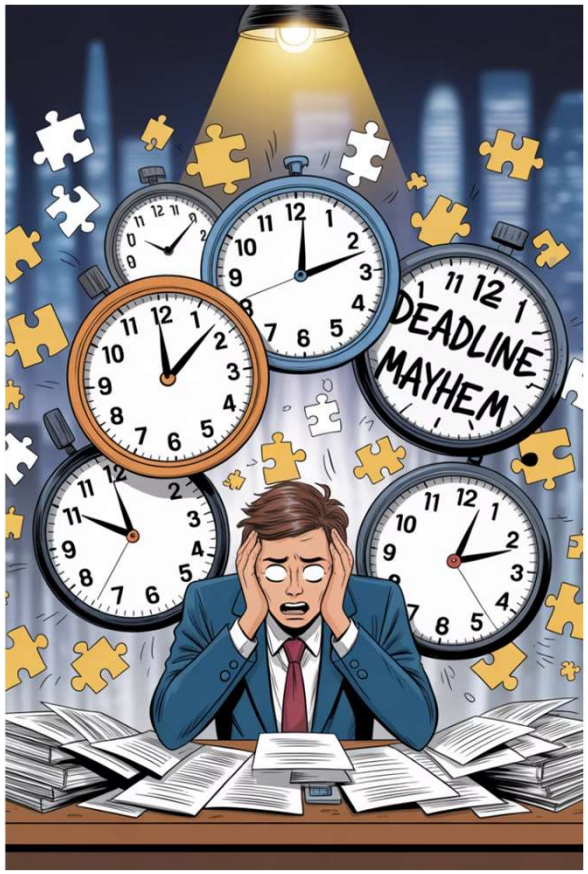
Clinical trials may not capture HTA-relevant endpoints, populations, key subgroups, or sufficient follow-up.

It could lead to post-hoc adjustments (e.g., ML-NMR) fraught with uncertainty, weakening negotiating leverage.

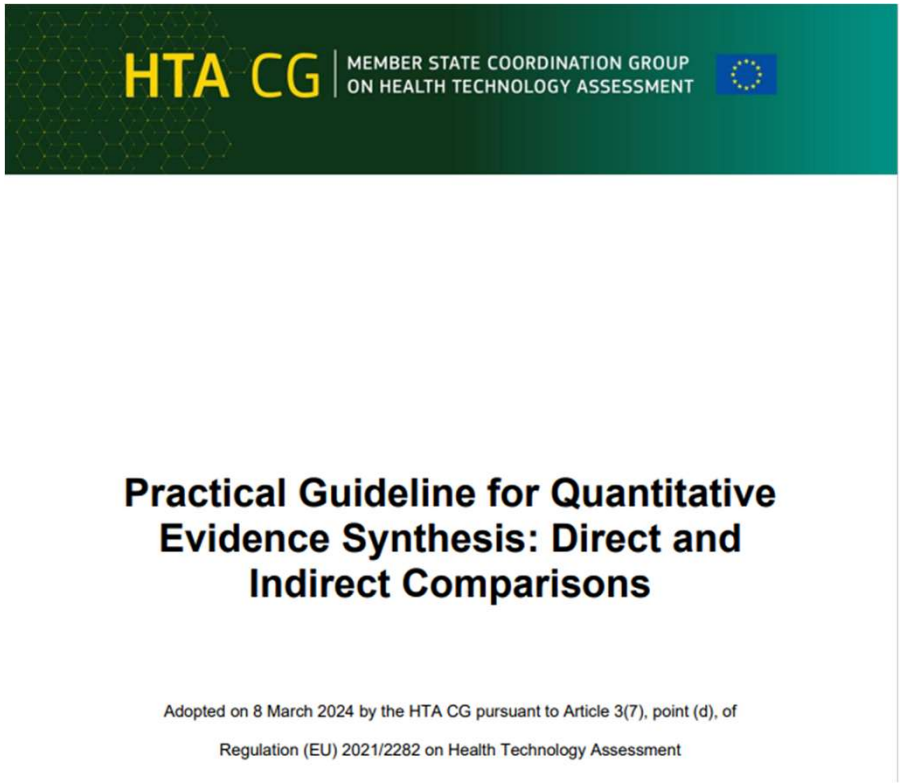
2. Last-Minute Crunch

Rushed ITC work around pivotal readouts is stressful, error-prone and/or lead to suboptimal choices of method.

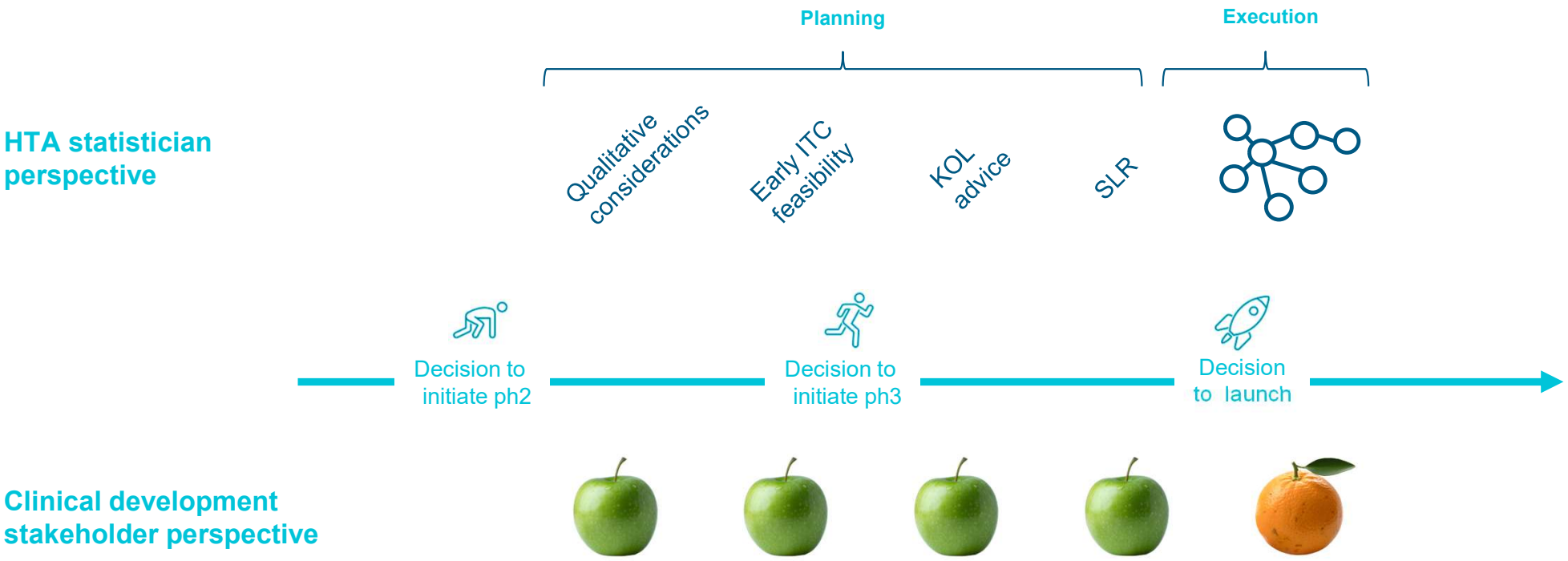
Risks missing critical deadlines



EU HTA prompts us to think about the foundation



But indirect evidence discussions may not be very accessible to non-technical stakeholders



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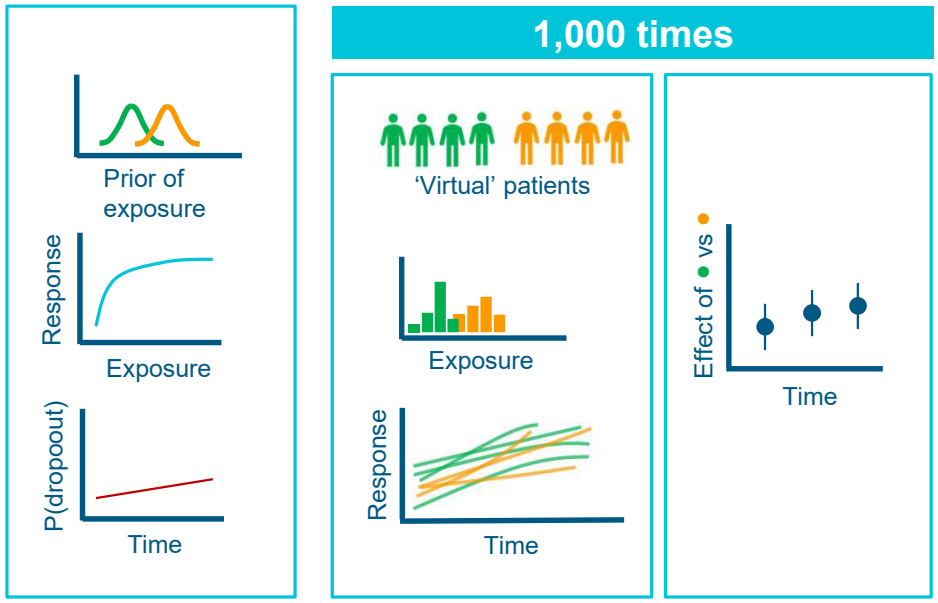
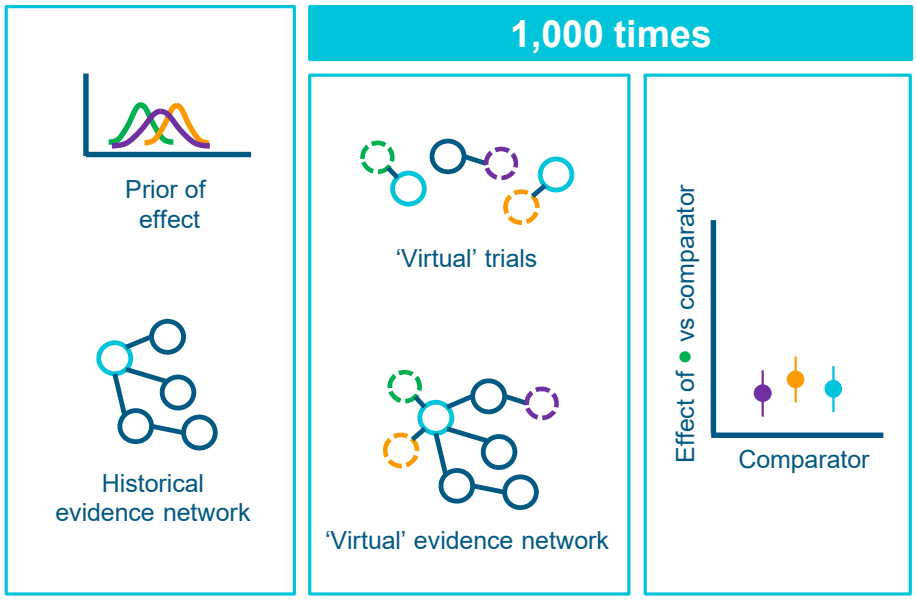
ITC quantitative scenario planning – game changer to drive accessibility of ITC discussions?

CLINICAL TRIAL SIMULATION



'ITC SIMULATION'



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Quantitative scenario planning can facilitate stakeholder dialogue & systematic tackling of '***what if...?***' questions

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Simulated dialogue with Stakeholders

"Do you really need a head-to-head trial – can't you just do an ITC?"

"What if we narrow the trial population wrt. a known effect modifier?"

"Can't you just use [insert favorite innovative statistical method] to fix this?"

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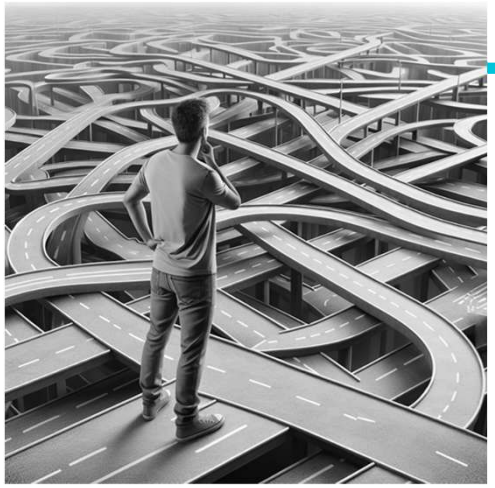
Why isn’t everyone doing this already?



Resource Constraints

Budgets and headcounts already stretched, leaving little room for additional early-stage work

Uncertain ROI

hard to justify the upfront investment, sunny projections can look cloudy in practice

Complexity Concerns

Juggling extra datasets and cross-functional inputs

Comfort Zone

Established workflows are comfy slippers, and switching to new shoes—even shinier ones—takes time and effort

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A New Opportunity for Statisticians to showcase Leadership, Best Practices, and Tech Savvy?

Proportional Effort

Allocate resources across development stages to focus only on HTA-critical decisions at each step.

Modular Workflows

Break ITC processes into reusable components (data prep, matching, analysis, reporting).

Agile Updates

Implement continuous-integration for data and models—iterate as new information arrives rather than waiting for a full pivot readout.

Simulated Dry-Runs

Run planned ITC methods on simulated datasets well before readouts—so adapting to actual data is straightforward. This is likely needed for mid-stage quantitative scenario planning, one can hit two birds with one stone.

Automation & Templates

Develop scripts, macros, and report templates to reduce manual effort.

Leverage Open-Source

Adopt or contribute to community tools to avoid rebuilding from scratch and stay up to date with best practices.

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R Consortium HTA working group

Working Group of industry, academia, HTAB participants, inspired by EU HTA JCA challenges and opportunities.

Initial workstreams:

- *Mapping of stakeholders, landscape and opportunities: to strengthen the shared understanding of challenges and potential solutions*
- *Package mapping : develop an inventory of HTA-related R packages related to HTA analytics, facilitating use and integration in daily practice*

https://github.com/RConsortium/HTA-wg

Conclusion: bridging innovation with application in ITCs

- *Less tooling, more schooling*
- Proactive integration of ITC thinking in drug development
- Quantitative scenario analysis as a bridge
- Cross-company collaboration opportunity
- Software engineering as an enabler

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Better methods or better planning?

Improving HTA decision-making

Keith Abrams

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ML-NMR – Improving HTA decision-making? 1

- What does a methodologist HTA DM look for in a 'new' method?
  - Does it answer an important question/address an important challenge? YES!
  - Does it appear to be complexity for complexity's sake? NO!
  - How does in compare to other methods?
    - Case studies
    - Simulation studies

ML-NMR – Improving HTA decision-making? 2

- What does a HTA DM look for in a ‘new’ method?
  - Does it answer an important question/address an important challenge? YES!
    - We want to compare multiple treatments simultaneously in a target population allowing for population differences in the evidence base.
  - Does it make assumptions which are reasonable? YES!
  - Does it provide results which can be easily understood/used? YES!
  - Does it provide results which other methods fail to do so? YES!

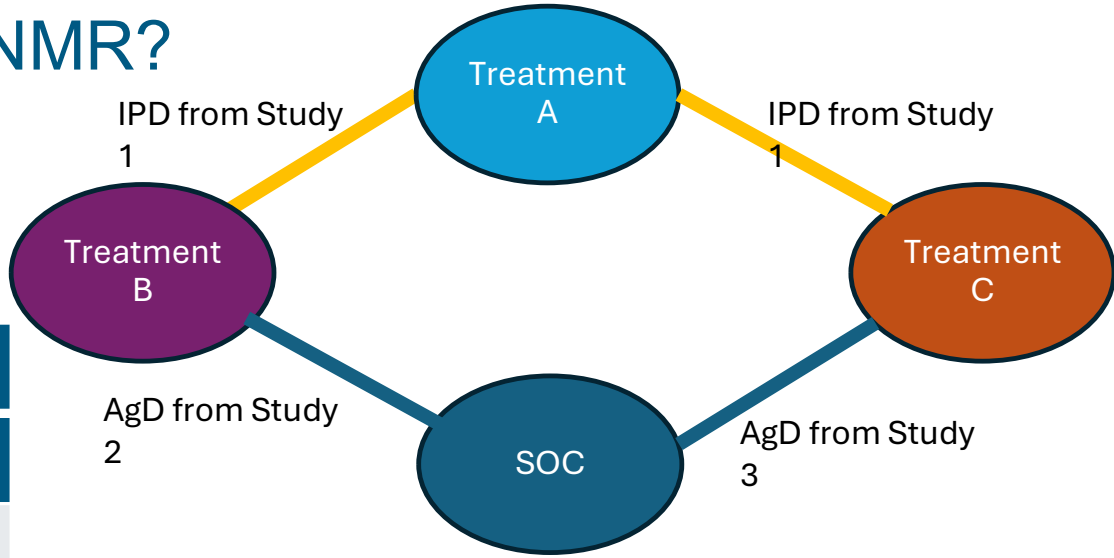
ML-NMR – Improving HTA decision-making? 3

- Consider …
  - "A is as effective as B … C is as effective as D… E is at least as effective as A."
  - "…(is) A as effective as, or inferior to C … (is) E as effective as D or not"
  - "two further questions on indirect comparisons arise, whether C is superior to A or not. and whether E is as effective as C or not."
  - This is actually from a NICE TA on thrombolytic treatment in 2003 before NMA was understood or accepted, BUT it could equally apply to a series of MAICs/STCs in 2025!
  - So MAIC/STC *versus* ML-NMR *cf.* pairwise MA versus NMA

ML-NMR – Improving HTA decision-making? 4

- Are there problems with ML-NMR?
- Consider …

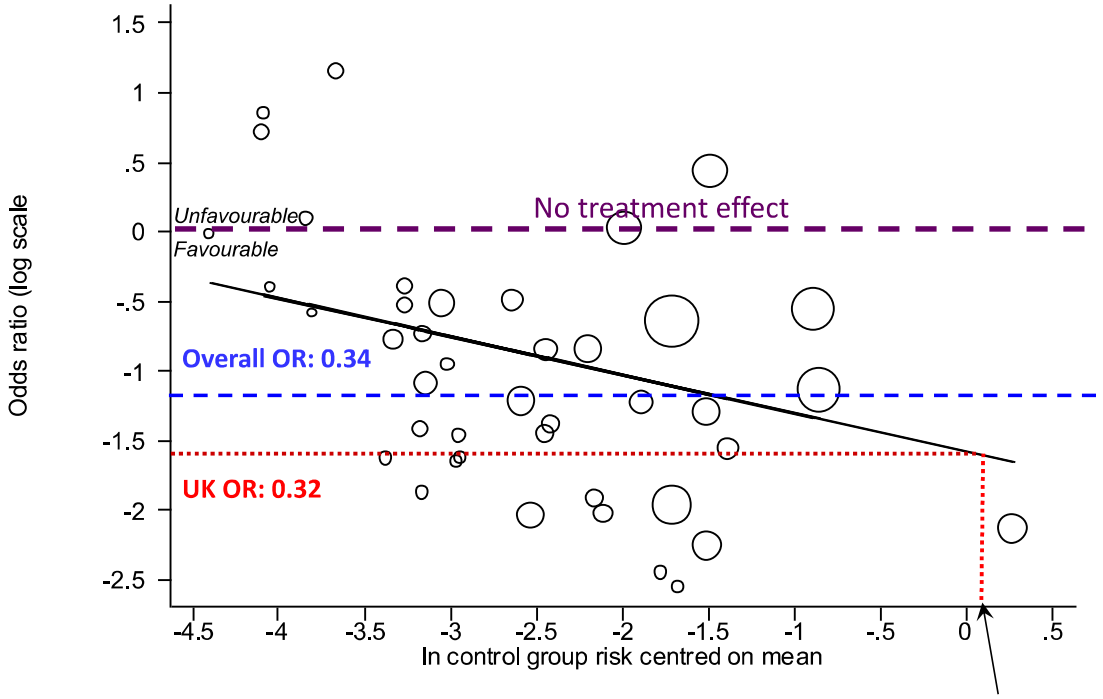
Study/Data	IPD		AgD	
Covariate	A-B	A-C	B-SoC	C-SoC
X_1	✅	✅	✅	✅
X_2	✅	✅	✅	❌
X_3	✅	✅	❌	✅
X_4	✅	✅	✅	✅



Solutions?

ML-NMR – Improving HTA decision-making? 5

- Other approaches to consider …



Baseline-risk/Control/Placebo effect adjusted MA/NMA

- Does not require covariate information
- (Target) Populations are often defined/described by 'risk'
- RTE are often applied to a natural history 'risk' in economic models

Achana FA *et al*. (2013) Extending methods for investigating the relationship between treatment effect and baseline risk from pairwise meta-analysis to network meta-analysis. *Statist Med*,32:752–771. https://doi.org/10.1002/sim.5539

ML-NMR – Improving HTA decision-making? 6

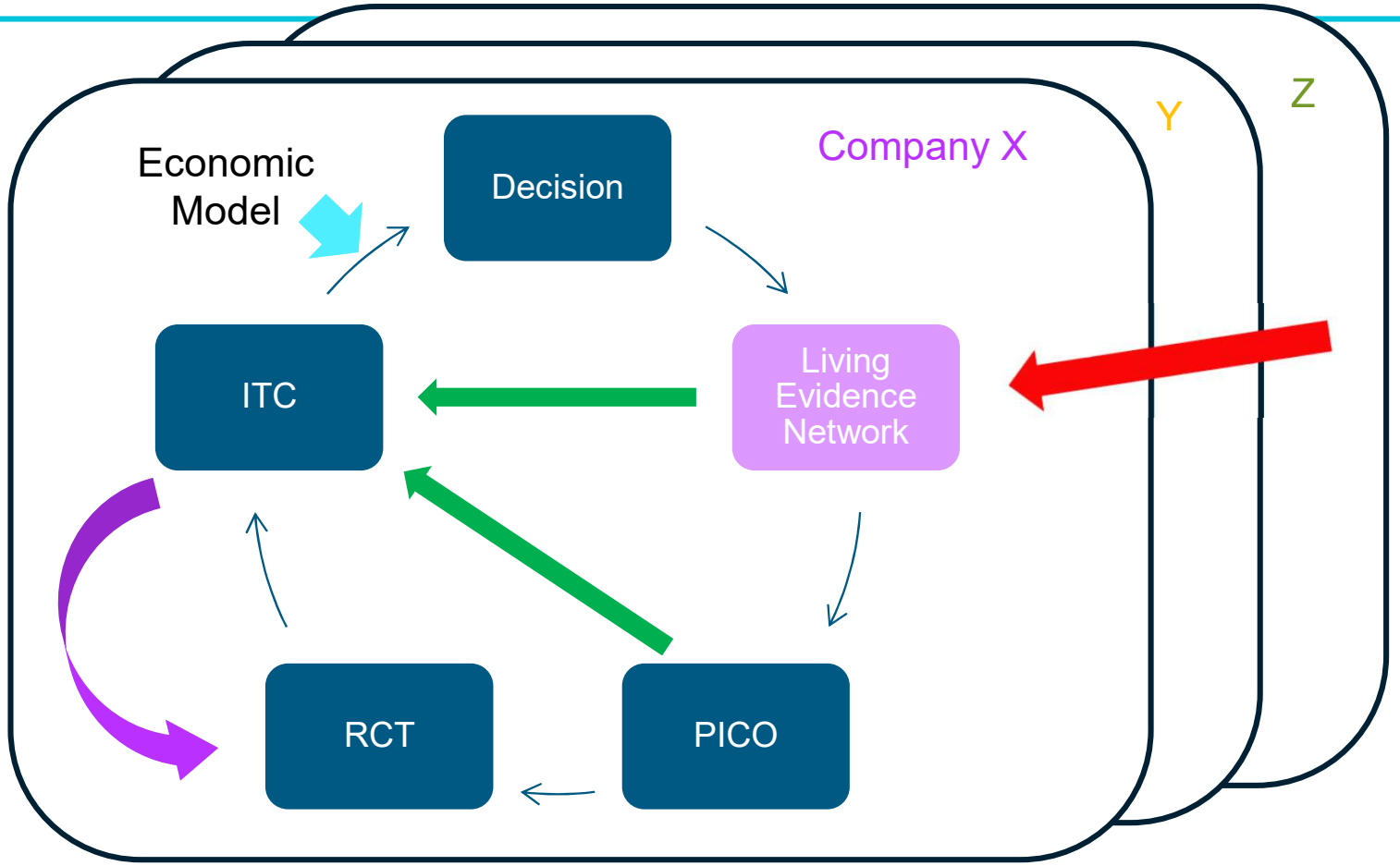
- When an assessors looks at all these ITC results and evidence: What are their thoughts?
  - If you want to convince assessors of what evidence/ITC is required: Is the evidence presented *appropriate* to decision problem and complexity of analyses proportionate?
  - Could we expect differences in NICE/JCA assessment? Possibly (though perhaps less so than previously in EU) – decision space *versus* evidence space, but this should be less crucial if *living evidence network*

ML-NMR – Improving HTA decision-making? 7

- When an assessors looks at all these ITC results and evidence: What are their thoughts?
  - We should know at an early stage where we are going to face issues in the future – this includes in the design of RCTs and what RWD may be required
  - We want to avoid the situation where the ITC should solve problems that could have been addressed or at least identified at an early stage
    - Old RCT adage – always be wary of overly complex analyses!
  - Think of PICOs at an early stage and link these to the ITCs performed (and other studies/data and analyses!)
    - PICO-ITC *cf.* Target Trial Emulation(TTE)-RWD - both are frameworks not solutions!

ML-NMR – Improving HTA decision-making? 8

The *Dynamic* HTA Process



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"We are a community dedicated to leading and promoting the use of statistics within the healthcare industry for the benefit of patients."