Successful use of Bayesian Dynamic Borrowing Methods in Regulatory Settings

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GSK

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Successful use of Bayesian Dynamic Borrowing (BDB) approaches at GSK

FDA Approved Product Label

BDB primary analysis of real-world data led to the inclusion of BDB results in the FDA-approved label for maternal Boostrix vaccination

Pediatric Efficacy Extrapolation

BDB in a pediatric efficacy trial facilitated FDA approval of Belimumab for pediatric lupus

CDE Approved Product Label

BDB design used for a confirmatory bridging trial that supported the approval of Nucala for severe asthma in China.

Use of BDB by GSK project teams

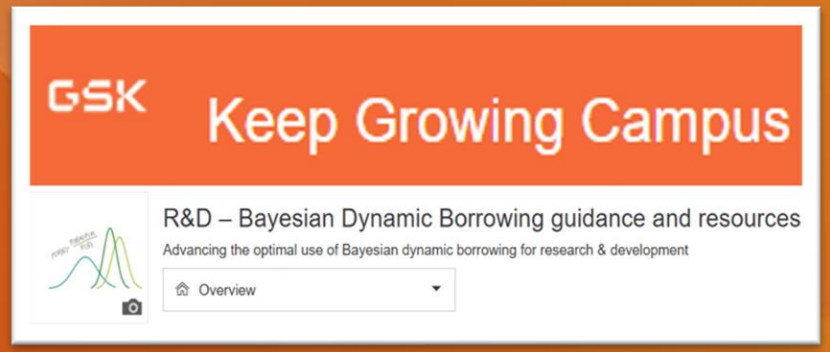
BDB is routinely considered for clinical efficacy extrapolation in paediatric studies at GSK

>30 project teams have considered BDB designs as part of their development plans

BDB = Bayesian Dynamic Borrowing

Road to “commercialisation”: Bayesian Dynamic Borrowing (BDB)

Bayesian Dynamic Borrowing resources, training, education and case studies at GSK



GSK BDB working group

Working group consisting of statisticians and regulatory team members to provide a one stop shop of BDB resources including:

- Points to Consider Guidance Document
- Dashboard and Case Studies
- Experiences of regulatory interactions
- Internal and External resources

GSK BDB working group – Points to Consider Document

IN WHAT SETTINGS CAN BDB BE USED?

- BDB can be used in all phases of clinical development covering both pre- and post-approval settings
- We can borrow information about an endpoint directly (e.g., an efficacy or safety endpoint on an active or control arm) OR we can borrow information about a comparative effect (e.g., treatment difference on active versus control)
- BDB can also be used to borrow information on more than one measure in the same study (e.g., in a paediatric trial, BDB could be used to borrow information on the placebo response from other studies in children, and information on the treatment effect from adult trials in the drug of interest)

- **To use BDB you must have some concurrent data on the quantity of interest**. Hence single arm trials with an external comparator arm (i.e., no concurrent controls) are out of scope for BDB

Figure 2: Common options for borrowing external information in different settings

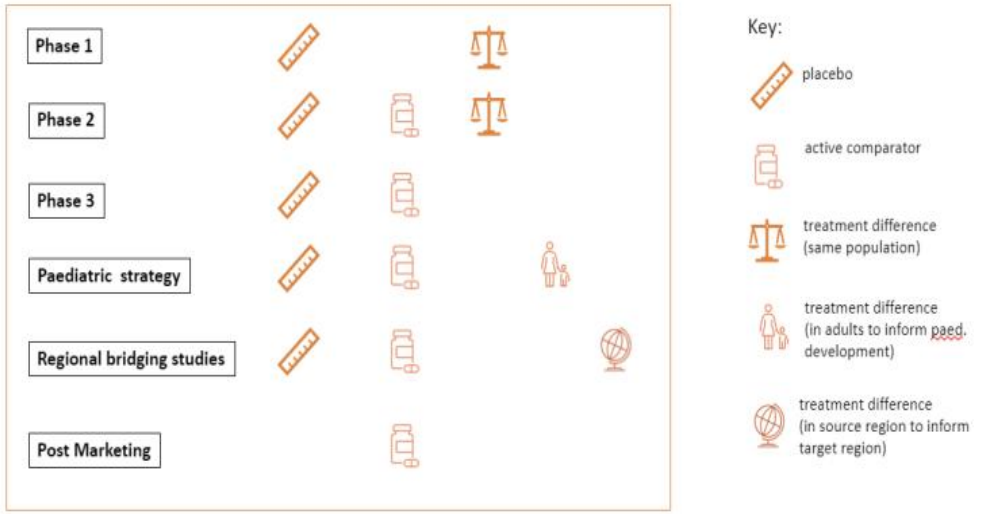
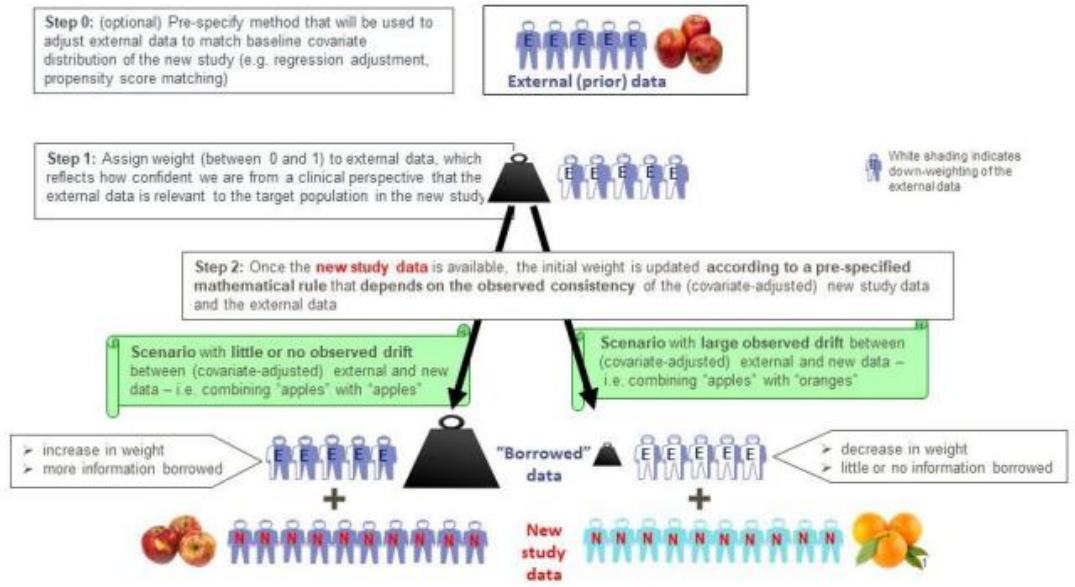


Figure 2 depicts the most common options for borrowing external information for standard types of studies. Note however that these suggestions are not exhaustive, not always technically feasible, and do not come with any guarantee of regulatory or payer acceptability. Indeed, each study comes with its own limitations and opportunities. For example, borrowing the treatment difference could also be technically implemented in Phase 3, but using such an informative prior in a confirmatory trial would typically have a very low probability of regulatory uptake outside of 'special' circumstances such as rare diseases. Similarly, a Phase 1 trial might often not have any subjects randomised to an active comparator, which therefore makes dynamic borrowing of active comparator data impossible to implement, etc.

Figure 1: Schematic illustration of how BDB works



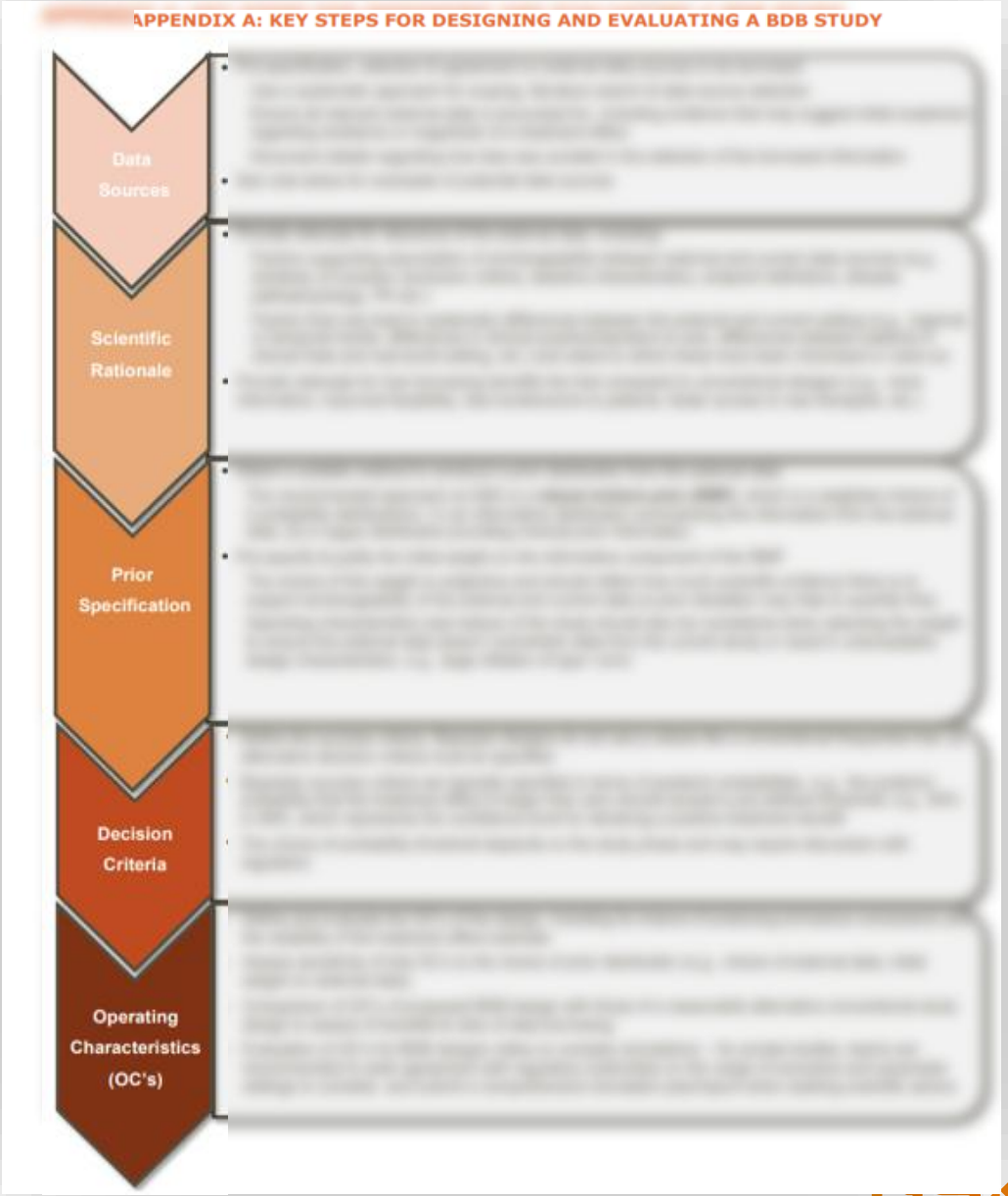
QUESTIONS FOR TEAMS TO CONSIDER AT EVERY PHASE OF STUDY

- Can we use historical or external data to reduce the sample size or improve power and precision?
- Are there barriers to using a standard design (e.g., difficulty enrolling study population) that could be mitigated by use of BDB?
- Are there opportunities to design the Clinical Development Plan to generate data in one study that can be borrowed in a subsequent study or phase?
- Do the benefits of using BDB outweigh the risks compared to a standard design/development plan?
- Do we need regulatory agency and/or HTA agreement regarding use of BDB, e.g., Scientific Advice?

GSK BDB working group – Checklist and Key Steps

DOs

- Provide a clear rationale for use of BDB
- Ensure acceptable balance of Type I error
- vs power compared to evidentiary standards
- Provide complete documentation, eg
  - Scientific rationale
  - Construction of the prior
  - Operating Characteristics



GSK BDB working group – Case Study Dashboard

Setting	Borrowing from / to	What is borrowed	Data borrowed	Objective / motivation for borrowing	Regulatory Agency	Regulatory feedback	Status of regulatory engagment
Paediatrics	from adults to adolescents	treatment effect (efficacy)	GSK internal	Fully powered study in adolescent population not feasible	FDA		Complete; Paediatric approval granted
Historical contorls (supportive analysis for secondary endpoint)	Historical control arm to current study	Mean QoL SF-36 Vitality score in control arm	External	Increasing precision of secondary endpoint for which the study was not powered for	FDA		Complete
Safety of new dosing regimen (historical controls)	Concurrent GSK study of a different dosing regimen of the same compound to current study	CV outcome rate in control arm (safety)	GSK internal	Avoiding having to run a CV outcome trials for a new dosing regimen	FDA		Complete

GSK BDB working group – Resources

- Regulatory guidance
- Publications
- Videos
- Training materials
- Other resources

Regulatory engagement with China Centre for Drug Evaluation

国家药品监督管理局药品审评中心
CENTER FOR DRUG EVALUATION, NMPA

GSK/CDE Webinar

Bayesian Dynamic Borrowing Design to Inform Regional Bridging Trial

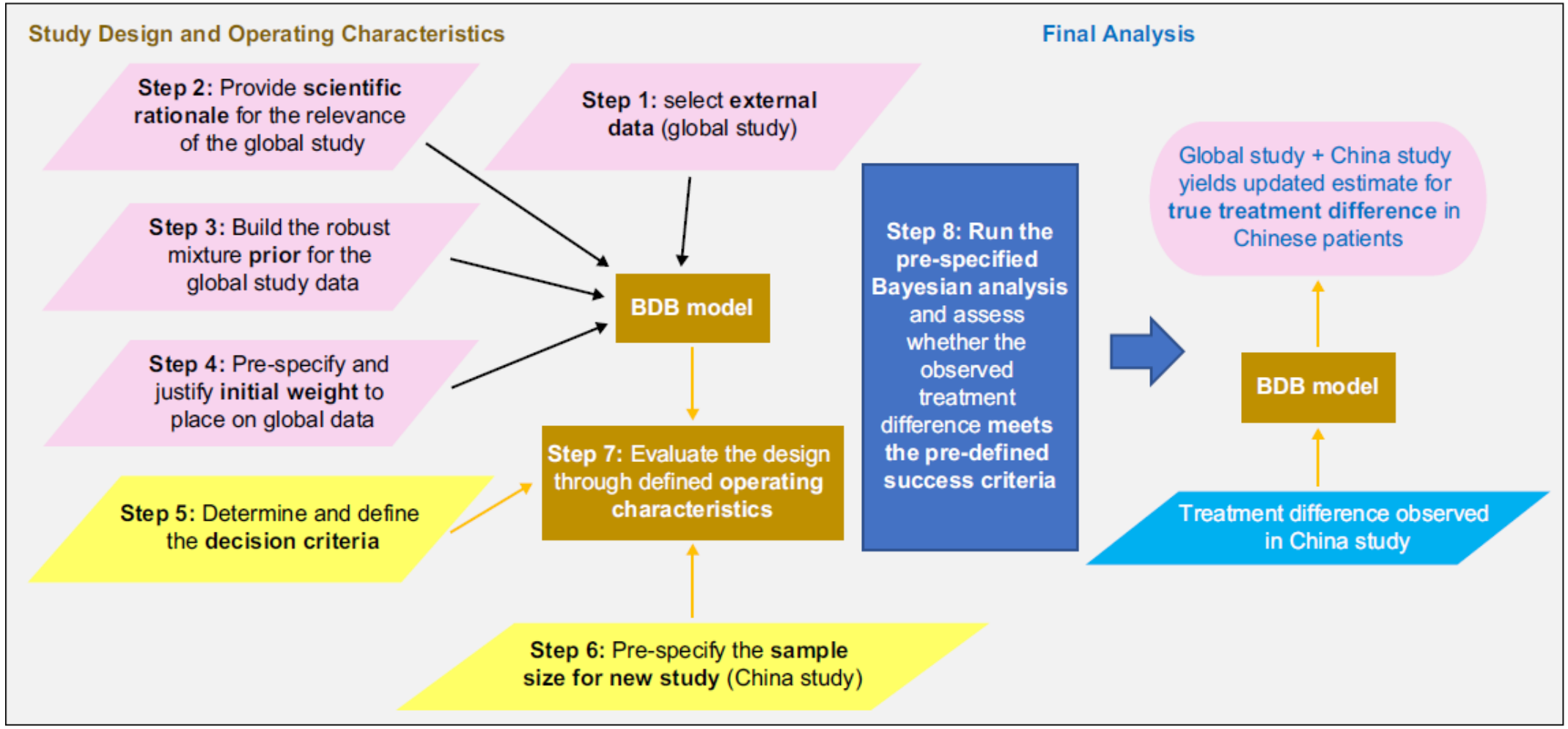
Agenda

- 15:00 BST/8:00 CST Introduction (Jun Wang and Yanmei Xu)
- 15:10 BST/8:10 CST Overview and Borrowing Information (**Chrissie Fletcher**)
- 15:25 BST/8:25 CST Concepts of Bayesian borrowing for bridging studies (**Nicky Best**)
- 16:10 BST/9:10 CST Case study: Trelegy bridging design (**Dawn Edwards**)
- 16:25 BST/9:25 Discussion (**All**)
- 16:55/9:55 Event Close

Using Bayesian Methods in Clinical Trials: A Regional Case Study

- Background:
  - Global study supported drug approval internationally, but no Chinese patients.
  - Separate study needed for registration with China's Center for Drug Evaluation
- Choice of BDB Approach:
  - Uses existing evidence from global study to supplement planned sample size
  - BDB likely to provide more robust evidence than unpowered standalone study
- Design of the China BDB Study:
  - Designed to closely replicate global study (incl/excl, primary endpoint, estimand)
  - Objective: Assess new v reference treatment for cts endpoint in Chinese patients
- Regulatory requirements:
  - Approach consistent with regulatory guidance at the time on Bayesian designs for drug approval (e.g. FDA Complex Innovative Designs, draft ICH E11A Pediatric Extrapolation) & with ICH E5 & E17 principles for bridging & multiregional trials

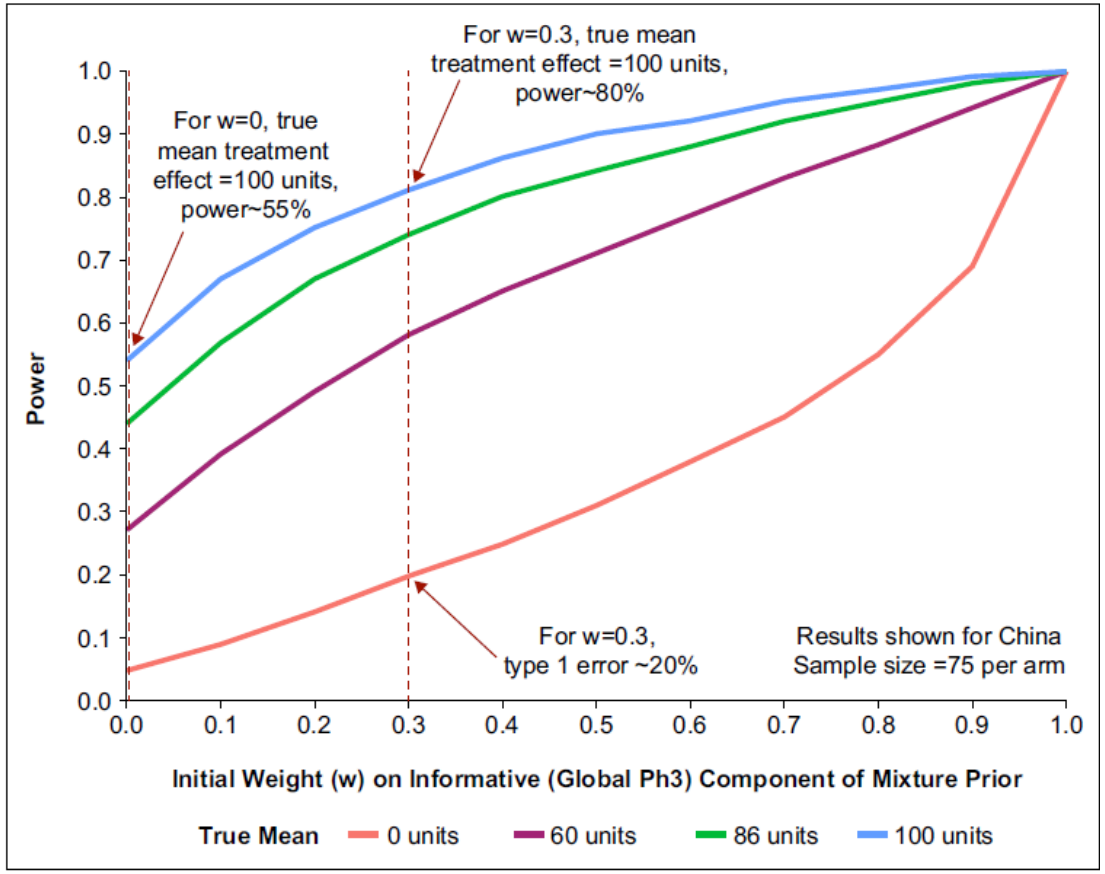
Study Design and Analysis Steps



Edwards D, Best N, Crawford J, Zi L, Shelton C, Fowler A. Using Bayesian Dynamic Borrowing to Maximize the Use of Existing Data: A Case-Study. Ther Innov Regul Sci. 2024 Jan;58(1):1-10. doi: 10.1007/s43441-023-00585-3. Epub 2023 Nov 1. PMID: 37910271; PMCID: PMC10764450.

Evaluation of study design operating characteristics

Power for new treatment versus reference treatment. *Ph3* phase 3, *W* weight.



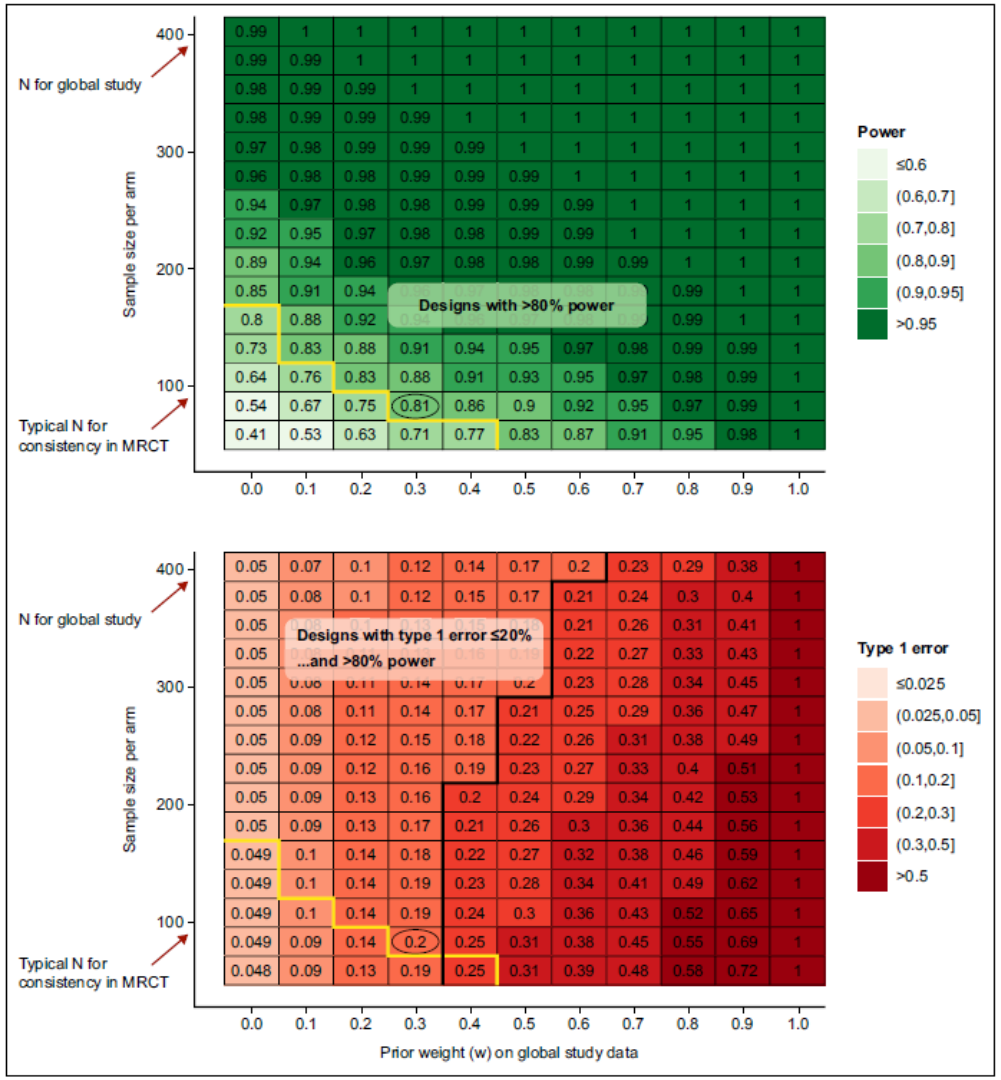


Illustration of operating characteristics to help select design parameters.

Operating Characteristics calculated using decision rule: Pr (treatment effect > 0) ≥ 95%, Power calculated assuming true treatment effect = 100 "units", Type I error calculated assuming true treatment effect = 0 "units".

Any combination of prior weight and sample size above the yellow line has power > 80% and anything to the left of the black line has type I error less than 20%. MRCT = multi-regional clinical trial.

Summary of Power and Type I Error Rate

Results based on using robust mixture prior with initial weight 0.3 on the global data which had an estimated treatment effect of 86 units

Operating Characteristic	Value	Commentary
Prob of a false positive result (assuming true treatment difference = 0 units)	20% (Type I error rate)	Increasing weight further would increase POS (type I error) above 20% As prior weight increases so does type I error—however, in bridging settings, there already is good prior evidence of treatment benefit, so risk of committing a type I error is low because likelihood that treatment is truly ineffective is low. A type I error of 20% for this study was considered reasonable
Prob of true positive result (assuming true treat difference = 100 units)	81% (Power)	If the true mean difference is 100 units (which is around what was believed to be the true treatment difference based on the global study), then the POS is 81%. Increasing weight has less significant impacts in further improving POS (i.e. the increase in POS plateaus)

Summary of the posterior distribution of true treatment effect given a range of hypothetical outcomes

(Observed Treatment Differences) in the China Study

Hypothetical outcome (Observed treatment difference) in China Bridging study	Updated (posterior mean) estimate of true treatment difference in China	90% Credible Interval for true treatment difference in China
0 units	43 units	(– 68 units, 105 units)
49 units	73 units	(> 0 units, 118 units)
60 units	77 units	(14 units, 121 units)
86 units	86 units	(38 units, 132 units)
100 units	90 units	(46 units, 143 units)

Results based on using robust mixture prior with initial weight 0.3 on the global data which had an estimated treatment effect of 86 units

China Case-study Conclusions

- BDB approach improved data use efficiency and reduced time, facilitating quicker availability of medicines.
- An alternative standalone study in China with trend analysis was considered but may have led to arbitrary treatment differences and reduced precision due to small sample sizes.
- Early interaction with regulatory agencies is encouraged to align objectives and address any queries.
- Collaboration with statistical experts also vital!

Bayesian Dynamic Borrowing (BDB) to support approval of Nucala for severe asthma in China

GSK's Nucala for severe eosinophilic asthma gains approval in China

The Nucala antibody targeting IL-5 was initially approved in the US for severe asthma with an eosinophilic phenotype.

January 11, 2024

Share

Bayesian Dynamic Borrowing (BDB) to support US Boostrix Maternal Immunization label

Background

- GSK seeking an additional indication for BOOSTRIX in US (specific formulation): maternal immunization during each pregnancy to provide passive protection against pertussis in early infancy.
- Pertussis affects about 7 out of 10,000 infants < 6 months each year in the US (rare event).
- Limited data on the effectiveness with the BOOSTRIX US formulation while several observational studies with the BOOSTRIX non-US formulation have shown effectiveness.
- The US Centres of Disease Control (CDC) conducted a case-control study to estimate the effectiveness of Tdap (ADACEL and BOOSTRIX) maternal immunization at preventing pertussis in young infants (Skoff, CID 2017). Inconclusive results (large variability).

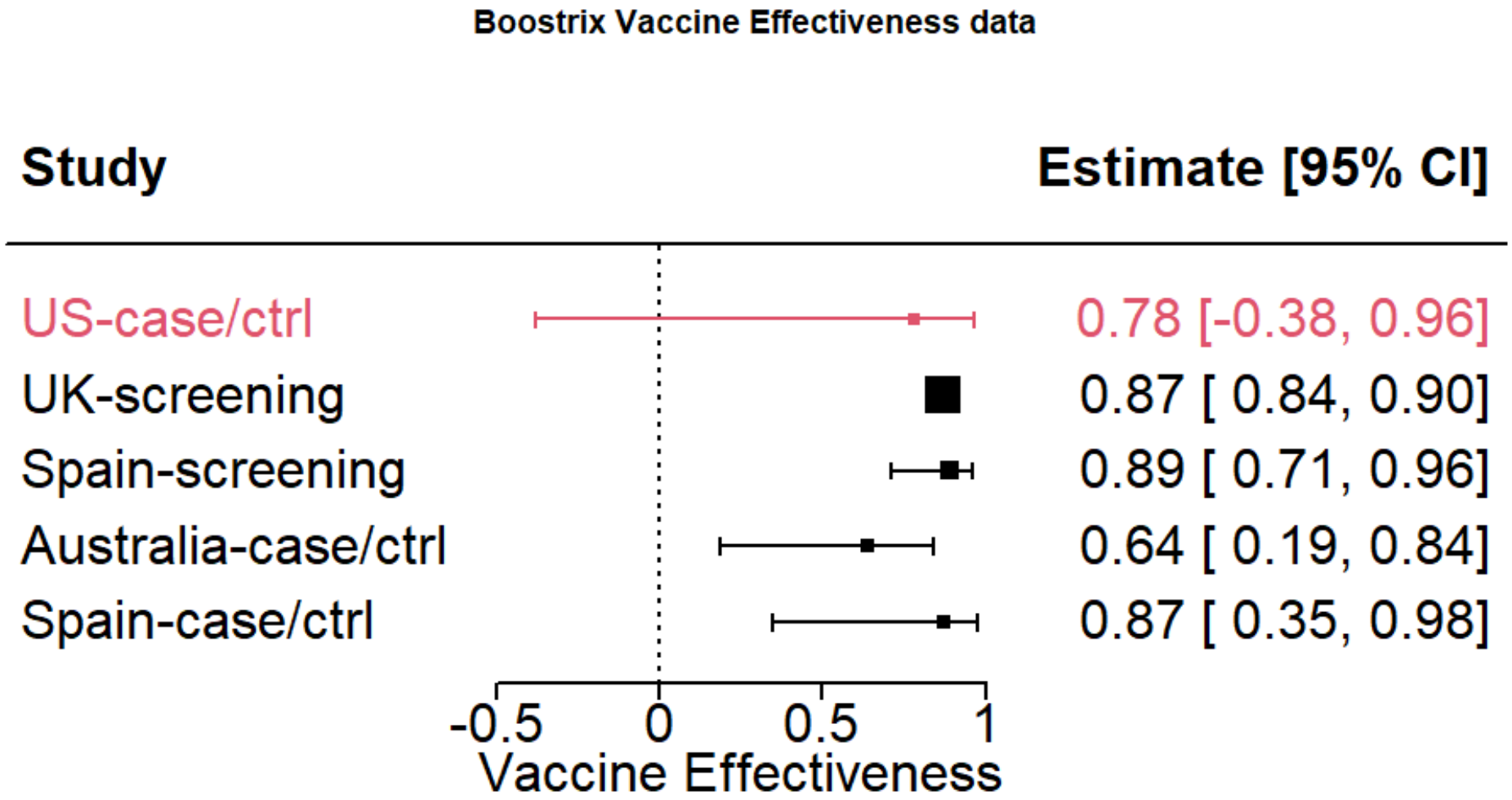
US Study (current data)

The US Centres of Disease Control (CDC) conducted a **case-control study** (Phase IV) to estimate the effectiveness of Tdap (ADACEL and BOOSTRIX) maternal immunization at preventing pertussis in young infants (Skoff, CID 2017).

While the point estimate of effectiveness supported the benefit of maternal immunization with BOOSTRIX, the large confidence interval did not allow to formally demonstrate the effectiveness (inconclusive results).

The US Centres of Disease Control (CDC) conducted a **case-control study** (Phase IV) to estimate the effectiveness of Tdap (ADACEL and BOOSTRIX) maternal immunization at preventing pertussis in young infants (Skoff, CID 2017).

Current (US) and historical (non-US) data



CBER interactions

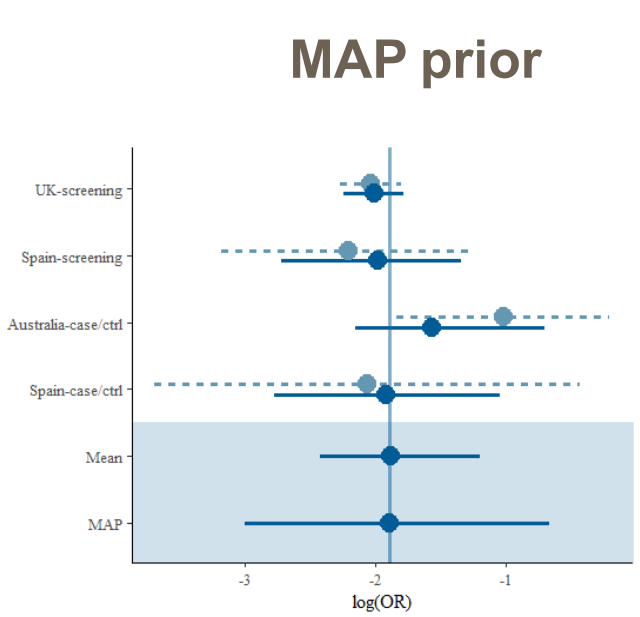
- Extensive and constructive exchanges were made between CBER and GSK to clarify the planned analysis and to provide ***sensitivity analyses***:
  - Effect on potential brand misclassifications in the US data
  - Effect of each historical study (leave-one-out meta-analysis)
  - Effect of the weight given to the prior (full range of w considered)

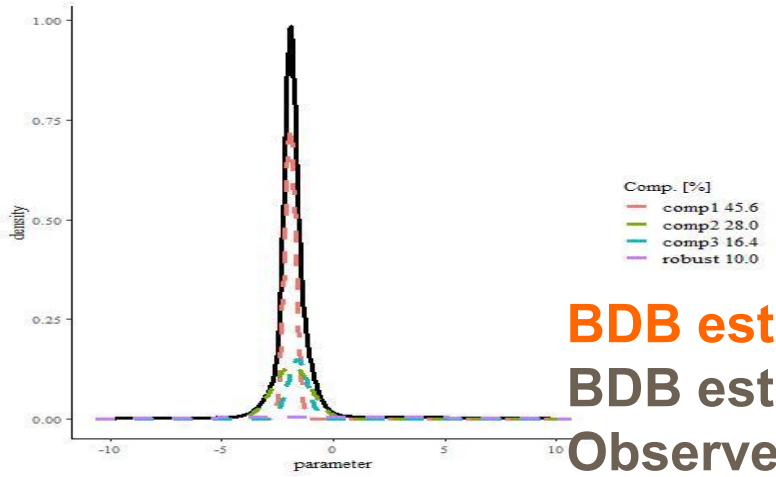
Table 1. BLA 125106/1469 IR Request Amendments

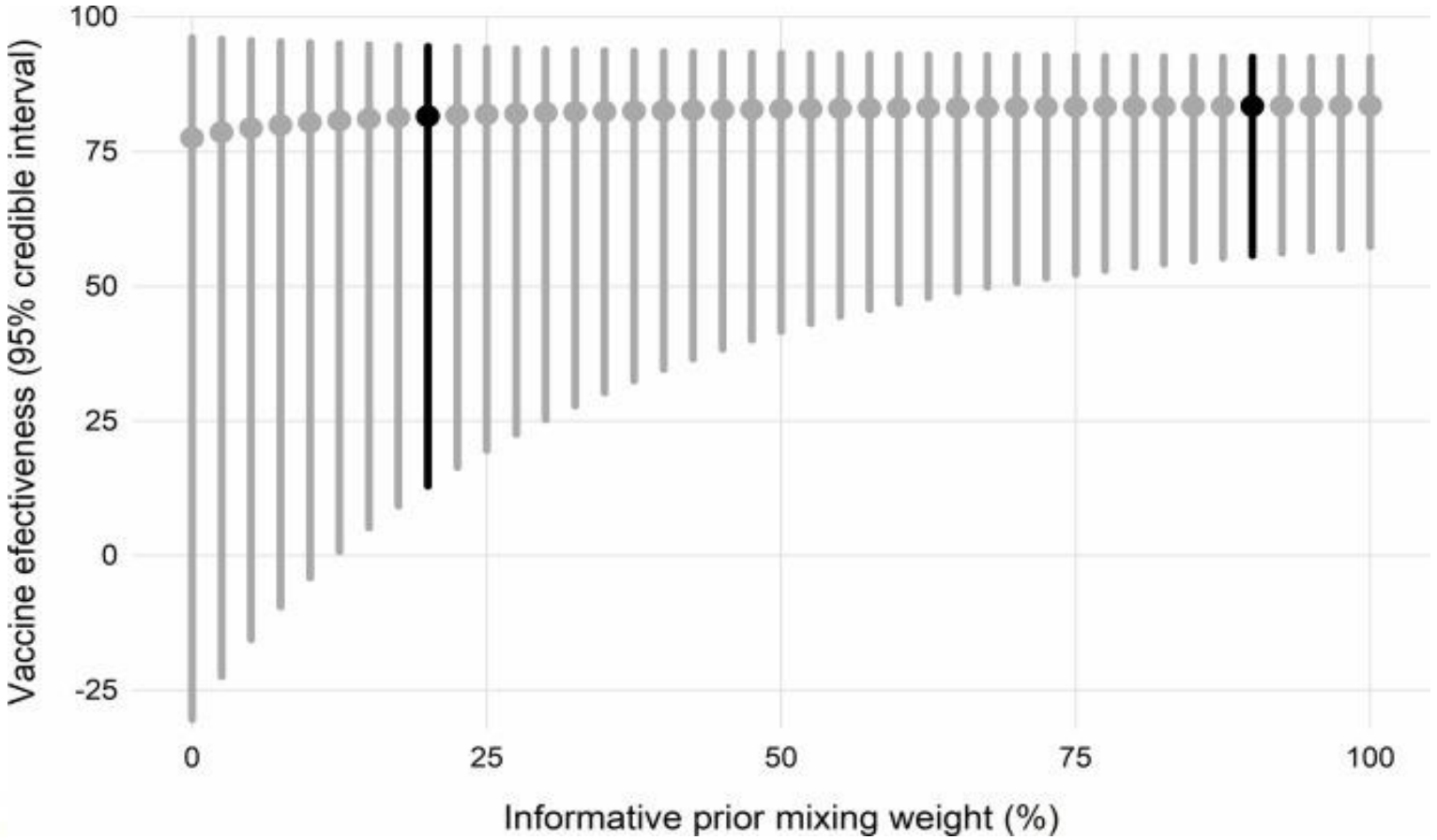
Amendment	Date IR Sent	Date Amendment Received	Summary
4	21 April 2021	05 May 2021	GSK's response to a request for a corrected systemic literature review figure, EPI-PERTUSSIS-052 dataset inconsistencies clarification
5	---	13 May 2021	CDC's responses to the 21 April 2021 IR added to GSK sub-amendment 4 responses
6	16 May 2021	01 June 2021	CDC's response to additional EPI-PERTUSSIS-052 dataset clarifications and GSK's sensitivity analysis results
7	29 June 2021	13 July 2021	GSK's response to additional EPI-PERTUSSIS-052 sensitivity analysis requests and dataset clarifications
10	24 May 2022	14 June 2022	GSK's response to request for revised EPI-PERTUSSIS-052 analyses using updated dataset
12	5 July 2022	19 July 2022	GSK's response to request for additional revised EPI-PERTUSSIS-052 analyses
16	17 August 2022	31 August 2022	GSK's response to package insert edits, including revisions to Section 14.3 description of the EPI-PERTUSSIS-052 analyses and results
17	9 September 2022	19 September 2022	GSK's response to package insert edits, including revisions to Section 14.3 description of the EPI-PERTUSSIS-052 analysis and results

Source: Created from the BLA 125106/1469 amendments

Robust MAP prior results







BDB estimate with 90% (pre-specified) weight: 83.4% [CI 55.7%; 92.5%]

BDB estimate with 20% weight: 81.5% [CI 12.9%; 94.5%]

Observed VE (US only): 78.0% [CI -38.0%; 96.6%]

Sensitivity analysis (leave-one-out meta-analysis)

Sensitivity analysis	VE (95% credible interval) Based on mixing weight of 90%.
1 (UK screening)	87.2 (39.5; 96.0)
2 (Spain screening)	79.7 (81.4; 90.5)
3 (Australia case/control)	83.3 (54.5; 92.4)
4 (Spain case/control)	73.7 (22.5; 88.1)

Boostrix Approved by FDA

- Boostrix pertussis received US FDA approval for immunization during pregnancy for protection of newborns against
- This is the first vaccine approved in US specifically for use during pregnancy to prevent a disease in young infants whose mothers are vaccinated during pregnancy
- First-ever inclusion of the BDB results in the label

trimester of pregnancy. This preliminary effectiveness estimate was updated using a Bayesian meta-analysis with an informative prior constructed from four observational studies that provided estimates of the vaccine effectiveness of the non-U.S. formulation of Boostrix against pertussis in infants whose mothers were immunized during pregnancy.[5, 6, 7, 8] To account for potential publication bias, this informative prior was downweighted by combining it with an uninformative prior. When the informative prior has 20% weight, the Bayesian update resulted in estimates of effectiveness of vaccination during the third trimester of pregnancy of 81.5% (95% credible interval:12.9, 94.5). When the informative prior has 90% weight, the Bayesian update resulted in estimates of effectiveness of vaccination during the third trimester of pregnancy of 83.4% (95% credible interval: 55.7, 92.5). The vaccine effectiveness point estimates were consistent, regardless of the weight applied to the informative prior.

Summary

- This BDB method is an attractive approach when estimating vaccine effectiveness against a relatively rare disease, with sample size challenges
- The choice of how much to borrow from the historical data should be carefully evaluated and needs to be approved by regulatory agencies
- Transparency and rapid response to CBER questions were drivers to the positive outcome
- Openness of CBER to innovations

The journey continues….

Questions?

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