Use of Bayesian Evidence Synthesis Techniques across Phases of Drug Development

Cory R. Heilmann
Eli Lilly and Company

Answers That Matter.

Outline

- Introduction and General Concepts
- Applications to Early Phase Studies
- Applications to Product Decision/Phase III
- Applications to Late Phase
- Conclusions

Introduction

Introduction: Critical Success Factors

- Critical Success Factor (CSF):
  - Attribute(s) that a drug must achieve to be successful from a specific trial or series of trials
- CSF as probability statement requires
- 1) a measurement e.g. QT interval
- 2) a statistic e.g. mean QT change from baseline or δ
- 3) a clinically relevant threshold e.g. $\delta < 10$ ms
- 4) a probability decision threshold e.g. $P(\delta < 10 \text{ ms}) > 90\%$
- CSF is central to decision making

Introduction: Motivation for Bayesian analysis

- CSF(s) inform future clinical development plan

Frequentist	Bayesian
Reject or fail to reject hypothesis	Probability that a hypothesis is true
With enough trials, the chance of false positive < α	Probability of success in subsequent trial is β
Base decision on single trial or meta-analysis	Flexible in incorporating different sources of data

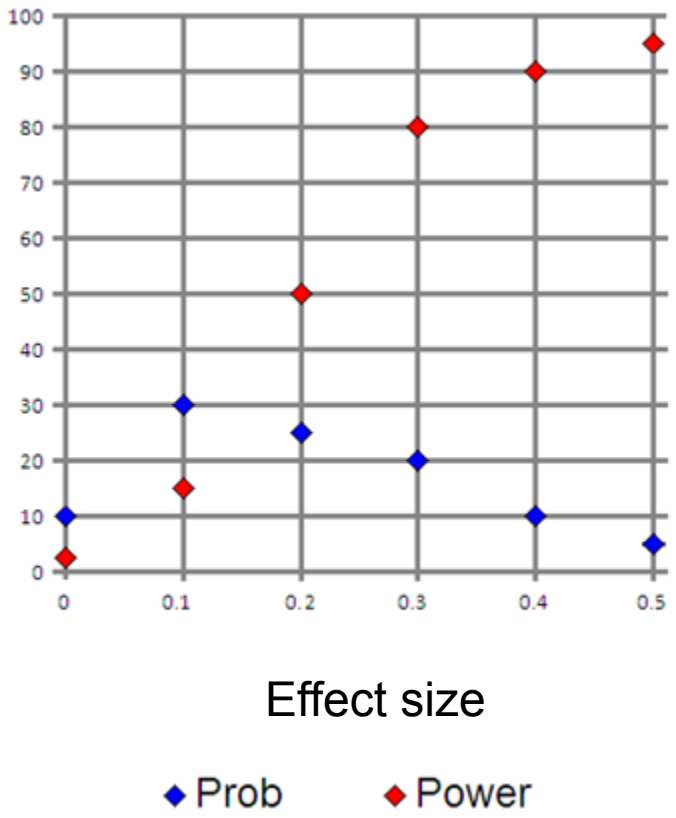
Introduction: Probability of Study Success (PrSS)

Power	Probability of Success
Assumes a effect size, variability, and dropout	Incorporates uncertainty about effect size, variability, dropout
Conditional on assumptions, study has x% chance to show superiority/non-inf	Incorporating all data, the probability of the study being successful is x%.

Introduction: Classical Power vs. PrSS

Effect Size	Probability of Effect size (Prob)	Conditional Power (Power)	Power* Prob
0.0	10%	2.5%	0.25%
0.1	30%	15%	4.5%
0.2	25%	50%	12.5%
0.3	20%	80%	16%
0.4	10%	90%	9%
0.5	5%	95%	4.75%

- 80% power assuming 0.3 effect size
- 90% power assuming 0.4 effect size
- 48% unconditional probability in this case



Introduction: PrSS

- “Success” may be measured differently in different phases
- In Phase 3/4 a study must hit primary objective to be successful
- In early phase, this is not as clear
- Consider:
  - A study which hits primary objective for a non-commercially viable compound
  - A study which fails primary objective and leads to termination of non-commercially viable compound

Introduction: PrSS

	Move to Phase 3	**Terminate before Phase 3**
Commercially Viable	Pr(True Positive)	Pr(False Negative)
Not Commercially Viable	Pr(False Positive)	Pr(True Negative)
Probability of Decision	Pr(Passing CSF)	Pr(Not Passing CSF)

- Can design studies to maximize decision making potential
  - Optimize trade-off between type I and type II error subject to constraints

Early Phase - Efficacy

- May have first study in population of interest
- Measure – likely a biomarker for a more robust parameter
- Need large enough magnitude of effect to give confidence of clinically meaningful response in larger study

Early Phase – Efficacy (example)

- Case example: Diabetes drug to lower blood glucose.
- Gold standard for efficacy: HbA1c at 6 months.
  - HbA1c is a measure of average blood glucose over 2-3 months
- Short Phase 2a study
  - 12 week study – not long enough for HbA1c for this drug
  - Measure fasting blood glucose (FBG) at 12 weeks

Early Phase – Efficacy (example)

- Need: Drug to show HbA1c reduction of at least 0.7%
- Equivalent reduction in fasting glucose ~ 21 mg/dL
- Confidence that 21 mg/dL reduction at 12 weeks leads to 0.7% HbA1c reduction at 24 weeks.

Early Phase – Efficacy (example)

- Developing the CSF
  - Statistically significant change in HbA1c may not be useful (may be well below the 21 mg/dL desired).
  - Also need confidence that effect size is clinically relevant
- Naturally leads to Bayesian framework

Early Phase – Efficacy (example)

- Consider:

$$\Pr(\Delta Y < -21 \text{ mg/dL}) > 70\%$$

- Specifically references the quantity of interest
- Sufficiently high probability

Early Phase – Efficacy (example)

- Model construction:
- $\Delta Y = \beta_0 + \beta_1 * Y_{BL} + \beta_2 * TRT + \varepsilon$
  - $\beta_0 \sim N(0, 1000)$
  - $\beta_1 \sim N(0, 1000)$
  - $\beta_2 \sim N(0, 1000)$
- If placebo response is consistent, consider informative prior on β_0

Early Phase – Efficacy (example)

- Considerations
  - Hurdle for efficacy – amount of information versus probability to claim success

Early Phase

- Early phase studies
  - Need to make informed decision
  - Both efficacy and safety are of importance
  - “Failure” can be a success (if failed studies leads to informed decision)
- If compound has clinically relevant effect, want to show that
- If compound does not have clinically relevant effect, want to show that as well

Early Phase

- Optimizing decision rule
- 70% probability of effect size of at least 0.7% sounds good
  - How likely are we to observe this event if the drug works “well”?
  - How likely are we to observe this effect if the drugs does not work “well”?
- Posterior probability does not directly answer this

Early Phase

- If effect size is lower than 15 mg/dL (less than 15 mg/dL decrease relative to placebo), want to terminate
- If effect size is greater than 24 mg/dL (more than 24 mg/dL decrease relative to placebo), want to proceed
- Between 15 mg/dL and 24 mg/dL, the decision is less clear

Early Phase

	Move to Phase 3	**Terminate Before Phase 3**
Commercially Viable	True Positive	False Negative
Unclear	Not certain	Not certain
Not Commercially Viable	False Positive	True Negative

Early Phase

- Can create decision rules
  - If effect size is 15 mg/dL, what is the probability of terminating? Of advancing?
  - If effect size is 24 mg/dL, what is the probability of terminating? Of advancing?
  - This information can complement the probability of clinically relevant effect size – threshold can be optimized based on False Positive/False Negative risk.

Applications to Product Decision/Phase III

Applications to Product Decision/Phase III

Phase I/II	Phase III
Need to develop proof of concept (POC)	POC established – need successful study(s)
Need results for future studies/product decision	Need results to submit for approval
Interested in probability of effect	Interested in PrSS

Applications to Product Decision/Phase III

- Network meta-analysis – also called mixed treatment comparison
- Typical Phase 2 study may be against placebo
- Phase 2 study may include a competitor
  - Typically, only 1 of many potential comparators
  - Often have low power to separate from (or even show non-inferiority to) competitor
- Need more information to design Phase 3 studies

Applications to Product Decision/Phase III - Example

- Situation: Diabetes compound (Drug X) - have phase 2b study against placebo
- Need to design phase 3 program – consider 4 competitor medications (Drug A, B, C, D)

Applications to Product Decision/Phase III - Example

- First step – literature review
- Crucial step
  - Failure to include studies may lead to bias
  - Including extraneous studies may also bias
  - Often need to consider posters or press releases, not just journal articles
  - May need to involve non-statisticians here
- Recommendation: Include as many studies as possible. Consider sensitivity analyses

Applications to Product Decision/Phase III - Example

- Mixed treatment comparison example
  - Project goal: To assess competitors' landscape oral diabetic agents and compare with phase 2 compound
  - Endpoint of interest: HbA1c
  - Competitors of interest

Applications to Product Decision/Phase III

- General mixed treatment comparison model: continuous variable.
  - Let Y_{jk} be outcome of interest for j^{th} treatment and k^{th} study
  - $Y_{jk} \sim N(\varphi_{jk}, \sigma/n_{jk})$ where $\varphi_{jk}=\varphi_k+\theta_j$
  - φ_k is a study effect and θ_j is a treatment effect
  - The unknown parameters are φ, θ and σ
  - We assume exchangeable (random) study effect $\varphi_k \sim N(\mu_\varphi, \tau_\varphi)$
  - We assume independent (fixed) treatment effect $\theta_j \sim N(\mu_j, \sigma_j)$ where μ_j and σ_j are constants

Spiegelhalter et al., *Bayesian Approaches to Clinical Trials and Health Care Evaluation*

Applications to Product Decision/Phase III

- Model the standard deviation (SD) for j^{th} treatment and k^{th} study, s_{jk}, as

$$\frac{(n_{jk}-1)s_{jk}^2}{\sigma^2} \sim \chi^2_{n_{jk}-1}$$

- Note that literature data will give summary level information so make sure to convert the standard error (SE) to SD i.e s_{jk} =sqrt(N/2)*SE

- It follows that

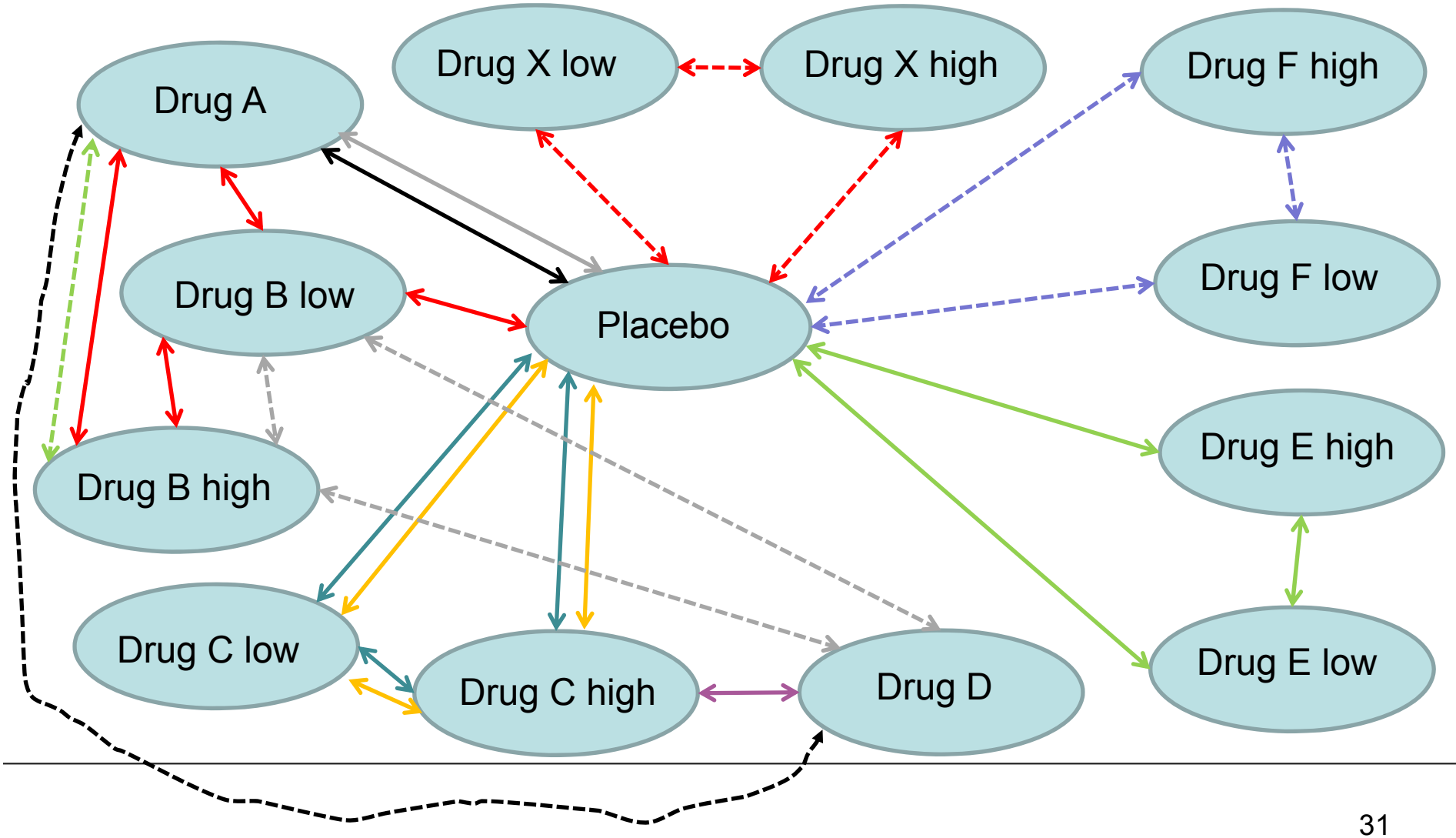
$$(n_{jk}-1)s_{jk}^2 \sim \Gamma((n_{jk}-1)/2,\ 1/(2\sigma^2))$$

Spiegelhalter et al., *Bayesian Approaches to Clinical Trials and Health Care Evaluation*

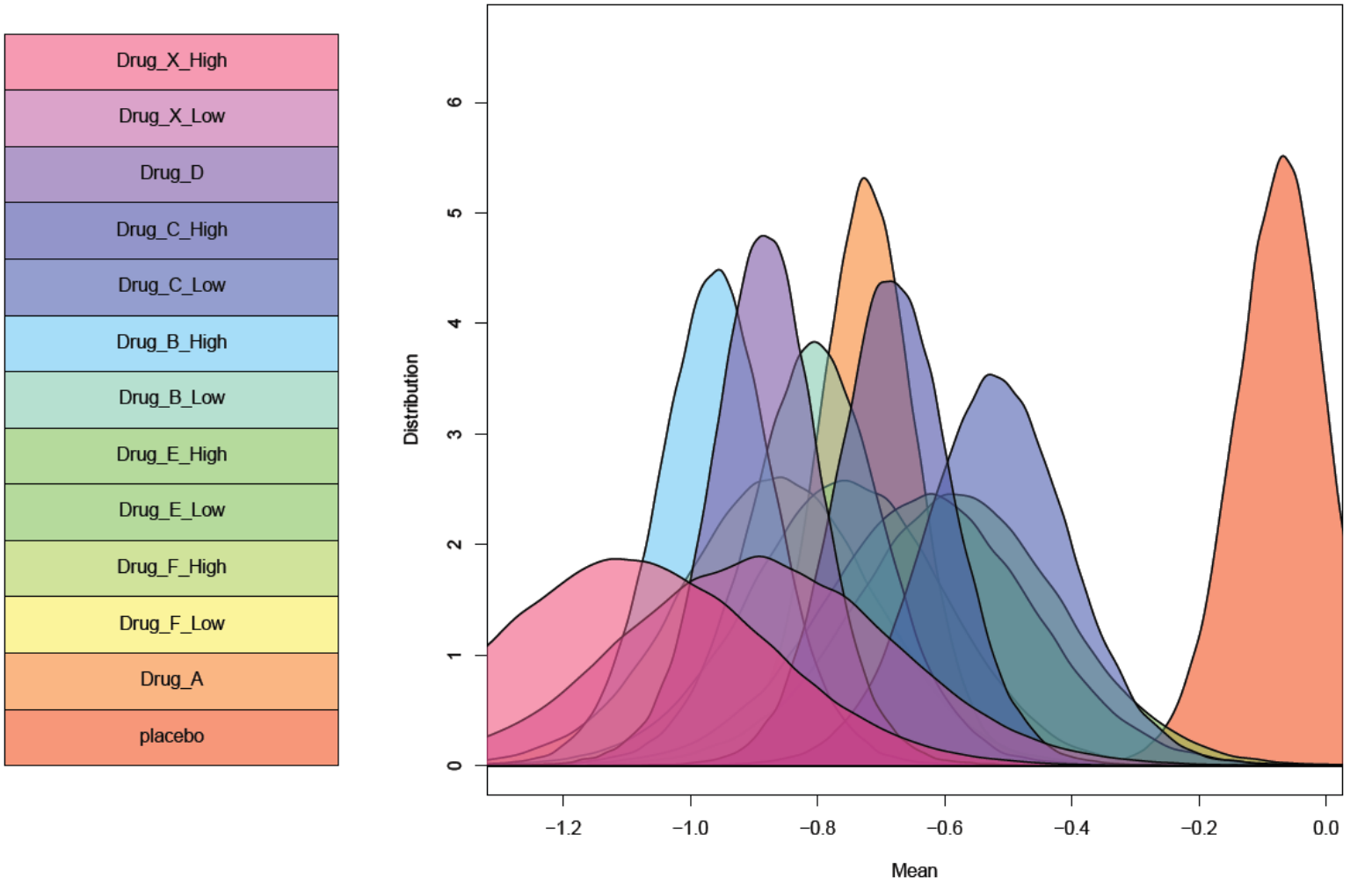
Applications to Product Decision/Phase III - Example

- Situation: Diabetes compound (Drug X) - have phase 2b study against placebo
- Need to design phase 3 program – consider 4 competitor medications (Drug A, B, C, D)
- Mixed treatment comparison is used, incorporating all Drug A, B, C, D, X studies, and also Drug E, F studies (which appear as comparator compounds)

Applications to Product Decision/Phase III - Example



Applications to Product Decision/Phase III



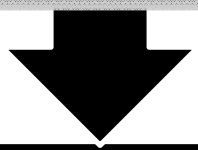
Applications to Product Decision/Phase III

- PrSS – Probability that study will be successful
- Interested in variable of interest (e.g. effect size) and how likely the phase 3 study will be to show this
- If effect size is favorable, but low chance to show this in phase 3
  - Terminate
  - Consider alternative design

Applications to Product Decision/Phase III

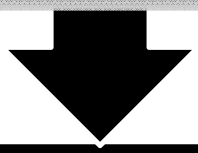
Prior information and phase 2 data

Prior information from compounds in the same class. One Phase 2 Study



Apply Bayes model using prior information and phase 2 data in Bayesian hierarchical model

This estimates the distribution of the parameters of interest.



Simulate future observations in ph 3 study, calculate Pr(CSFs)

This estimates the power of the Ph 3 studies, accounting for uncertainty in the hypotheses. Posterior prediction to inform the gatekeeping strategy.

Applications to Product Decision/Phase III - Example

- Information from mixed treatment comparison is useful, but not sufficient.
- Need to inform future studies
  - Important consideration is probability of study success in phase III

Applications to Product Decision/Phase III - Example

- Simulate phase 3 study from posterior samples given by the MTC
  - MTC shows uncertainty of the true effect size
  - Need to simulate individual studies to incorporate sampling variability
  - May need to incorporate inconsistency of MTC matrix – not just describe it

Applications to Product Decision/Phase III

- Other issues to Phase III programs
  - Phase III studies are pivotal for approval (and costly)
  - Secondary variables may be key to differentiation
  - Benefit/risk may be important
  - Need to consider probability of study success
    - Tailor CSFs accordingly

Applications to Product Decision/Phase III - Example

- Phase 3 studies have primary objective – “gold standard efficacy”
  - Often superiority/non-inferiority with standard margin or effect size
- Need to control Type 1 error rate for label claims
  - Gatekeeping and possible combination with Hochberg (or other) mutliplicity adjustments
- Combination of importance of claim and likelihood to observe claim are relevant

Applications to Product Decision/Phase III - Example

- Diabetes example – primary is non-inferiority with margin of 0.3% (HbA1c)
- Consider weight reduction, hypoglycemia, or superiority for secondary objectives
  - Variables may be related

Applications to Phase IV

Applications to Phase IV

- Network meta-analyses are key for reimbursement OUS
- NICE has extensive technical documents regarding these
- http://www.nicedsu.org.uk/Evidence-Synthesis-TSD-series%282391675%29.htm

Applications to Phase IV

- Safety detection/evaluation (e.g., AERS data).
- Use in observational studies – particularly in unmeasured confounding

Conclusions

- Bayesian techniques are applicable across phases of drug development
- Early phases – internal decision making
- Post approval – greater ability to influence externally
- Crucial to understand assumptions
  - Requires statistical, therapeutic area, and business knowledge