Using Statistical Principles to Implement FDA Guidance on Cardiovascular Risk Assessment for Diabetes Drugs

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Lilly
Answers That Matter.

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Outline

1) Review of FDA Guidance Documents
2) Description of Phase 2 and 3 Studies
3) Statistical Approaches to Cardiovascular Outcomes Study
4) Statistical Approaches to Meta-Analyses
5) Including Cardiovascular Outcomes study into the Meta-Analysis
6) Conclusion

FDA Guidance Documents

FDA Draft Guidance Document (Feb 2008)

Title: Diabetes Mellitus – Developing Drugs and Therapeutic Biologics for Treatment and Prevention

Recommendations regarding exposure:

	Total Exposed	**≥ 1 year**	**≥ 1.5 years**
No. of Patients	2,500	1,300-1,500	300-500

FDA Guidance Document (Dec 2008)

Title: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

Provides recommendations on how to demonstrate that new antidiabetic therapies are not associated with an unacceptable increase in cardiovascular risk

Recommendations

- Independent CV Endpoints Committee adjudicates, in a blinded manner, CV events from Phase 2 and 3 studies

- Perform a meta-analysis of Phase 2 and Phase 3 studies (include placebo-controlled, add-on and active-controlled studies)

- Include patients at higher risk of CV events (elderly, relatively advanced disease)

- Likely need to increase duration of studies (> 6 months)

Statistical Assessment

- Compare the incidence of CV events of the investigational agent to that of the control group

- Using meta-analysis and/or a large safety trial, determine whether the Upper Bound (UB) of the 95% CI for the estimated hazard ratio is < 1.8.

- If the upper bound of the 95% CI is between 1.3 and 1.8, then a post-marketing trial will generally be necessary to demonstrate the estimated hazard ratio is < 1.3.

- If the upper bound of the 95% CI is < 1.3, a post-marketing trial will not generally be necessary.

Phase 2 and 3 Clinical Trials for Antidiabetic Therapies

Phase 2 and 3 Clinical Trials (General)

Relatively healthy diabetic patients (low CV risk, kidney exclusion)

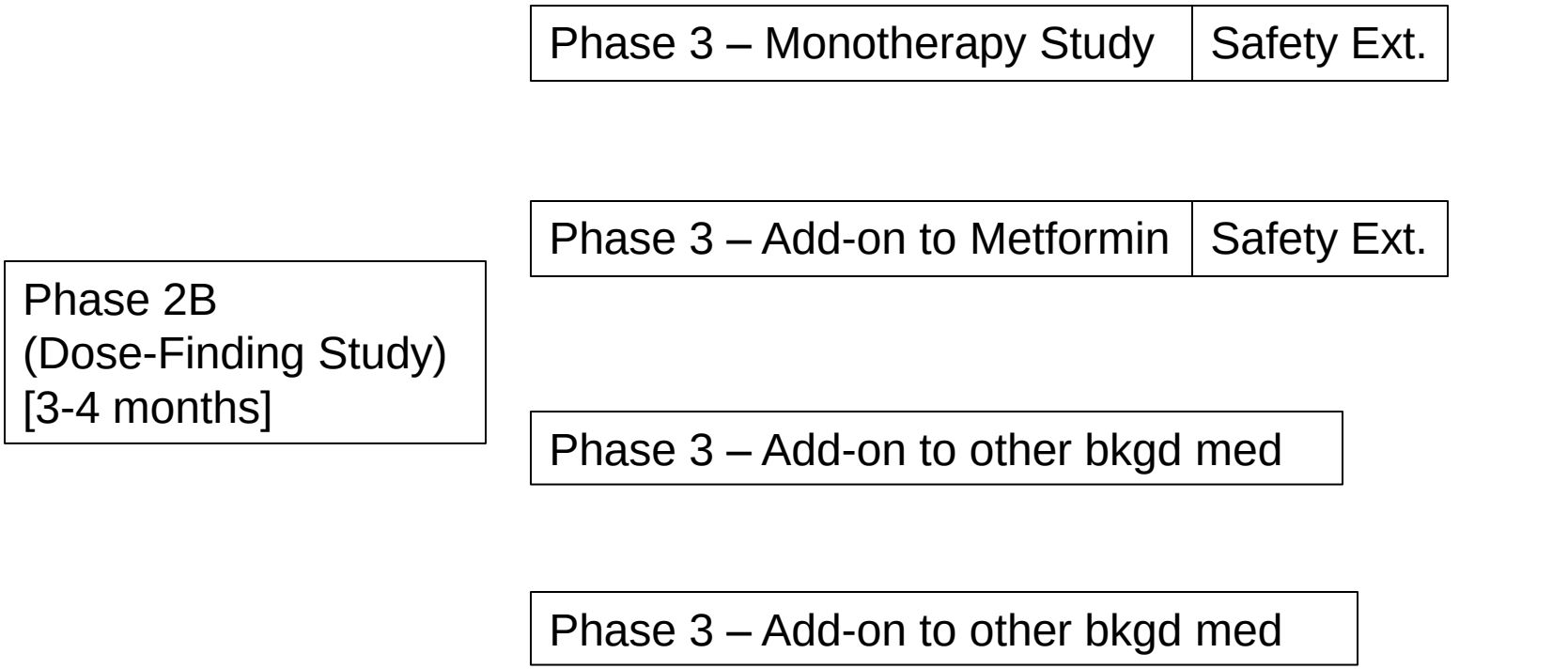
Low CV event rate

Duration (6-24 months)

Multiple dose levels of experimental drug

Background antidiabetic medication may differ between studies

Example Development Program



Compound Development Implications to conduct Meta-analysis

- Design Similar Studies:
  - Inclusion/exclusion criteria, target populations, blinding, randomization, duration of studies
  - Handling of rescue medication
  - Background medications
  - Follow-up on discontinued patients
  - Higher risk patients included
- Adjudicated CV Events (formation of Clinical Endpoint Committee)
- Statistical Analysis Plan for meta-analysis

Number of Events Needed

NI Margin	80% Power	90% Power
1.8	91	122
1.3	456	611

Assume 95% CI

Number of Patients Needed

Annual Event Rate (Drug)	Annual Event Rate (Control)	Total Sample size < 1.3		Total Sample size < 1.8	
		80%	90%	80%	90%
1%	1%	12,762	17,084	2,544	3,404
1.5%	1.5%	8,620	11,540	1,718	2,300
2%	2%	6,508	8,712	1,298	1,736

Assume 95% CI, 2 year accrual, 5 year maximum duration, 5% dropout rate per year, Equal Randomization

Recent Examples (Retrospective Analyses)

Liraglutide:

Total Number of Patients on Liraglutide: 4,257

Total Number of Patients on AC or PL: 2,381

38 total events (0.57% event rate)*

*Custom MACE, Population B

Saxagliptin:

Total Number of Patients on Saxagliptin: 3,356

Total Number of Patients on AC or PL: 1,251

40 events (0.87% event rate)*

*Custom MACE

How to get Sufficient Number of CV Events?

Options:

- Increase duration and patient numbers in phase 3 clinical trials
- Enroll higher risk patients in phase 3 studies
- Start CV Outcomes Study at the time phase 3 studies begin

CV Outcomes Study

CV outcomes Trial

Decide on Composite Endpoint (MACE, MACE +1, etc.)

- MACE (Myocardial Infarction, Stroke, and CV mortality)
- Example of MACE + 1 (Myocardial Infarction, Stroke, CV mortality, hospitalization for unstable angina)
- Other possibilities for “+1” component of composite endpoint

Parallel, two-arm study, diabetic patient population

- Increased CV risk (CV history, elderly, etc.)

CV Outcomes Study

Survival Analysis methods used

Statistical power driven by number of events (not number of patients)

Goal : We want to show Upper Bound of 95% CI is < 1.3

Given the number of events, the actual number of patients needed will depend on enrollment pattern, drop-out rate, follow-up time, and event rates

Two big questions:

What is the event rate?

What is the true hazard rate?

CV Outcomes Study (Cont.)

Possible Approaches:

Approach #1: Assume “worst case” hazard rate and event rate to determine number of events needed

- Problem: Possible to greatly inflate number of patients needed unnecessarily

Approach #2: Assume “optimistic” hazard rate and event rate to determine number of events needed

- Problem: Possible to have very low power

Use Sample Size Reestimation (Frequentist or Bayesian)

CV Outcomes Study (Cont.)

Sample Size Re-estimation (Frequentist Approach):

- Bauer and Kohne approach (1994)
- Divide Study into 2 Stages (Example Only):
  - Stage 1:
    - Perform Interim analysis when 33% of the information (events) is available
    - Spend small amount of alpha (0.0001) since purpose is SSR not stopping study
    - Calculate Conditional Power and determine number of patients needed to randomize to achieve desired conditional power

CV Outcomes Study (Cont.)

- Stage 2:
  - Enroll more patients
  - Final Analysis: combine evidence from both stages to make inference
  - Use p-value combination approach

CV Outcomes Study – Bayesian Approach

Approach proposed by Dr. Jason Connor (from Berry Consultants, Inc.) at Bayesian Biostatistical Conference 2009

Goal: Estimate CV event rate during the study in order to estimate the needed sample size

<u>Background:</u>

Assume events follow exponential distribution

Prior: $\lambda_t \sim \Gamma(0.001, 1)$

Likelihood: $X_{i,t} \sim \text{Exp}(\lambda_t)$ for $t \in \{0, 1\}$

CV Outcomes Study – Bayesian Approach (Cont.)

Background (Cont.):

Suppose we observe EV_t events in EXP_t days of follow-up

Posterior: $\lambda_t \mid \text{Data} \sim \Gamma(0.001 + EV_t, 1 + EXP_t)$

Calculate posterior distribution for λ_1 / λ_0

Goal: Determine if 95% Credible Interval for λ_1 / λ_0 is < 1.3

CV Outcomes Study – Bayesian Approach (Cont.)

Perform Interim Analysis after xxx patients have enrolled

Calculate Predictive Probability of Trial Success – P_n

- Given current sample size
- If we stop enrolling now
- Wait 1 year
- Perform Final analysis (95% CI for λ_1 / λ_0 is < 1.3)

Calculation of P_n :

- Use patients currently enrolled who have not dropped out or had an event
- Simulate additional events per treatment group using updated event rates (assume exponential times to event)

CV Outcomes Study – Bayesian Approach (Cont.)

Define Success (S_n) and Failure (F_n) Bounds

Decision Rules :

- Stop Trial if $P_n < F_n$
- Stop Accruing Patients if $P_n > S_n$
  - Wait 1 year and do final analysis
- Keep enrolling if $F_n < P_n < S_n$
- Stop at a maximum sample size

CV Outcomes Study (Cont.)

In addition to SSR, consider other adaptive features:

- Perform interim analysis for futility
- Use of alpha-spending functions in case testing at multiple interims for UB < 1.8 or < 1.3 is needed

Meta-Analysis

Advantages of Meta-Analysis within a clinical development program

- Individual Patient Data (IPD) available
- Know date of event, so time to event analyses possible
- Events are adjudicated similarly
- Do not have publication bias issue
- Plan for the meta-analysis

Meta-Analyses (Background)

Fixed Effects Models

- Each study population has same true treatment effect (therefore, observed effect differences between studies are due to sampling error)
- Assume studies are relatively homogeneous (no differences in study populations, patient-selection criteria)

Random Effect Models

- Each study has a different treatment effect, however, these individual treatment effects are considered a random sample from a distribution with a true fixed treatment effect
- Does not assume studies are homogeneous

Sparseness of Events Issue

- Low CV event rate may lead to zero events in treatment arms or in entire study

- Exclude studies with zero events because they do not contribute much to the estimate of the treatment effect but can move treatment effect towards null hypothesis if included

Sparseness of Events Issue (Cont.)

- Include studies with zero events because they are providing information about event rates (sample size should be taken into account)
  - Use continuity correction factors to account for these studies

- For meta-analyses with rare events, fixed effects models are preferred (Sweeting, et al, Statistics in Medicine 2004)

Survival Analysis

Cox Proportional Hazard Model (stratify by study):

$$h_{ij}(t) = h_{oi}(t) \exp(\beta_1 x_{1ij})$$

where i=1,…, k (study)

j=1, …, n_i (patient)

$h_{oi}(t)$ is common baseline hazard for study i

β_1 is the log-hazard ratio

Note: Stratify by study because different patient populations may not satisfy proportional hazard assumption

Proportional Hazard Model and Testing for Homogeneity

Using Stratified Cox PH model, does not allow one to estimate the effect of the strata variable (study in this case)

Homogeneity can be tested by including a study-by-treatment interaction term into model

Note: This test has low statistical power

Binary Analysis

- Important: Stratify by study
- Fixed Effects Models:
  - Mantel-Haenszel (MH) method
  - Inverse variance (IV) weighted method
  - Peto method
  - Logistic Regression
  - Bayesian method
- Random Effects Models:
  - DerSimonian and Laird (DL) Method
  - Logistic Regression
  - Bayesian Method

Continuity Corrections

- Continuity Corrections:
  - Add 0.5 to each cell
  - Treatment arm continuity correction
    - Choose a proportionality constant *k*
    - Add *k* / (Sample size for Opposite Treatment Arm) to each cell
    - May be less biased when severe unbalance
  - Empirical continuity correction
    - Estimate odds ratio of non-zero studies
    - Takes into account imbalance between treatment groups
    - Assume corrections sum to 1 and solve for each

Comparison of Binary Methods

- Pay attention to group imbalance and sparseness of events

- When group imbalances occur, the MH, IV and DL methods are biased with Continuity Corrections of 0.5

- The MH approach provides the least biased results with group imbalances with either the treatment arm or empirical corrections

- Peto method increases in bias with larger group imbalance

- Logistic regression and Bayesian fixed effects models perform consistently well

Including Cardiovascular Outcomes Study into Meta-Analysis

Two Tests of Hypothesis

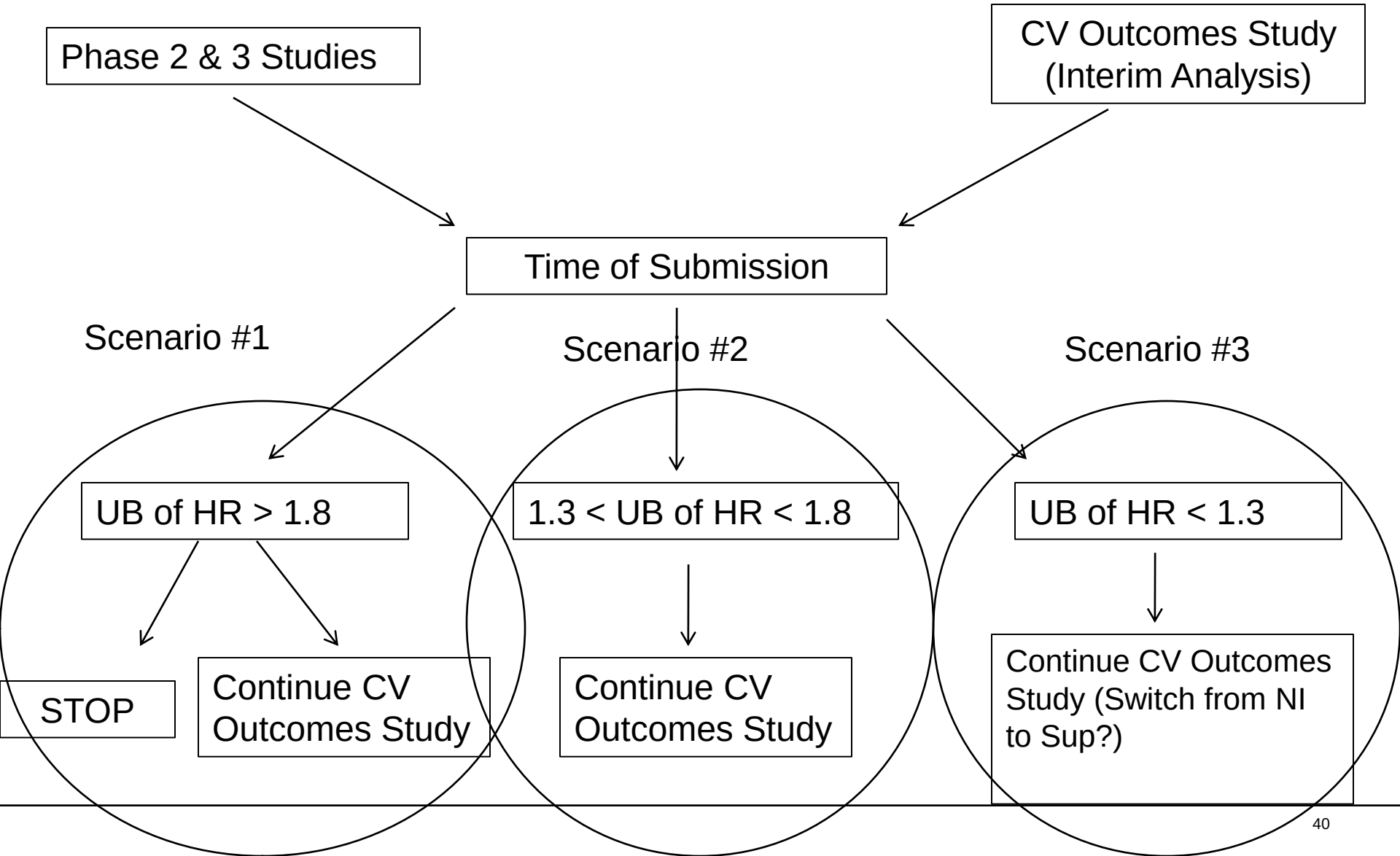
#1: Test the Upper Bound of the 95% confidence interval is < 1.8

- Spend 0.05 alpha for this test

#2: Test the Upper Bound of the 95% confidence interval is < 1.3

- Spend 0.05 alpha for this test

Submission Strategy (Meta-Analysis)



Scenario #1: What if Upper Bound of HR is > 1.8?

Possible Options:

- Stop Development
- Continue CV Outcomes Study
  - If point estimate of hazard ratio is not very high
  - Perform another interim analysis in CV Outcomes Study to demonstrate UB is < 1.8 (adjustment of alpha is necessary)
    - If the UB < 1.8 has been demonstrated at an interim analysis, then use final analysis to test whether UB < 1.3
    - If at conclusion of CV Outcomes Study only the UB < 1.8 has been demonstrated, then a new post-marketing study will need to be started

Scenario #2:
What if 1.3 < Upper Bound of HR < 1.8 ?

Complete CV Outcomes study to demonstrate UB of hazard ratio is < 1.3

If at completion of CV Outcomes study, the UB is > 1.3, then start new post-marketing study (assuming point estimate is not very high)

Scenario #3:
What if Upper Bound of HR < 1.3

Strategy/Analysis Options:

Stop CV Outcomes Study

Continue CV Outcomes Study to confirm < 1.3

Switch CV Outcomes Study from Non-Inferiority to Superiority (assuming point estimate < 1)

Analysis Questions

Should meta-analyses continue to be performed to demonstrate UB < 1.8 with each interim analysis in the CV Outcomes Study?

Should meta-analyses be used to demonstrate UB < 1.3 at conclusion of CV Outcomes study?

Conclusions

The FDA guidance documents have definitely impacted development of new antidiabetic medications

- Greater scrutiny of CV risk
- Higher risk patients included

Different meta-analysis approaches can be used :

Preferred: Survival Analysis

Sensitivity Analysis: Binary Outcomes

Conclusions (Cont.)

Different statistical approaches can be used to design CV Outcomes study (especially with uncertainty around event rates)

Make allowances in design for adaptation:

- Sample size reestimation
- Adjustment of Type 1 error for multiple interim analyses
- Futility Analyses

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