FDA and BRAT Frameworks for Structured Approaches to Benefit-risk Assessment

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American Statistical Association and Bayer HealthCare Workshop

Statistical Perspectives and Challenges in the Evaluation of Benefit-Risk for the Development of New Drugs

November 8, 2013

Disclosures

- Bennett Levitan is employed by, and owns stock in, Janssen R&D, a health care company developing rivaroxaban (XARELTO), an anticoagulant for the treatment of various thromboembolic diseases, and numerous other pharmaceuticals.

- Bennett Levitan is invested in financial portfolios that own stock in companies undertaking clinical development of pharmaceuticals.

Structured Approaches to Benefit-risk Assessment

- **Becoming increasingly important in sponsor and regulatory benefit-risk assessment**
- **Several industry and regulatory initiatives are developing structured approaches to benefit-risk**
  - FDA
    - CDER B-R framework under PDUFA V
    - CDRH B-R Guidance
  - ICH
    - E2C(R2) guidelines on Period B-R Evaluation Reports (PBRER) – replacing Periodic Safety Update Reports (PSURs)
  - EMA
    - B-R Methodology Project
    - 80-day assessment template
    - Pharmacovigilance legislation implementing PBRERs
  - Health Canada
    - Draft guidance for post-market B-R assessment
  - PhRMA
    - BRAT Framework → CIRS UMBRA framework
  - IMI PROTECT project

Agenda

- **FDA Benefit-risk Framework**
  - With acknowledgement to Patrick Frey
- **BRAT Framework**

Driver Behind FDA Framework

- **Prescription Drug User Fee Act (PDUFA)**
  - Law that authorizes FDA to collect fees from drug developers
  - FDA must meet goals agreed upon by developers and FDA

- **FDA Commitments for Benefit-risk Under PDUFA V**
  - Publish a 5-year plan that describes FDA's approach to implement a structured benefit-risk framework and begin execution by September 30, 2013
  - Conduct two public workshops on benefit-risk from the regulator's perspective
  - Develop an evaluation plan to ascertain the impact of the benefit-risk framework
  - Revise review templates, decision memo templates and MaPPs to incorporate FDA's approach

Framework Development

- **Used case studies of prior regulatory decisions to develop a conceptual framework**
  - Conducted interviews of key review disciplines on select challenging, less obvious decisions to identify the range of benefits and risks
  - Developed question-based prompts to guide Framework completion
- **Pilot-tested the framework in on-going pre-market reviews**
  - Evaluated and further refined the Framework and the question-based prompts
  - Focused on implementation of the Framework in the review process

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Summary of evidence:	Conclusions (implications for decision):
Current Treatment Options	Summary of evidence:	Conclusions (implications for decision):
Benefit	Summary of evidence:	Conclusions (implications for decision):
Risk	Summary of evidence:	Conclusions (implications for decision):
Risk Management	Summary of evidence:	Conclusions (implications for decision):
Benefit-Risk Summary and Assessment		

FDA's Benefit-risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Summary of evidence:	Conclusions (implications for decision):
Unmet Medical Need	Summary of evidence:	Conclusions (implications for decision):
Clinical Benefit	Summary of evidence:	Conclusions (implications for decision):
Risk	Summary of evidence:	Conclusions (implications for decision):
Risk Management	Summary of evidence:	Conclusions (implications for decision):

FDA's Benefit-risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Summary of evidence:	Conclusions (implications for decision):
Unmet Medical Need		
Clinical Benefit		
Risk		
Risk Management		

- Scientific evidence
- Capture range of FDA expert opinion

- Implications, given FDA regulatory mandate
- Inform FDA decisions

- **Analysis of Condition**
  - Describe the condition treated or prevented by the drug
  - Clinical, natural history, variance across sub-populations, affect on QOL?
- **Unmet Medical Need**
  - SOC, other therapies including approved and off-label pharmacological and non-pharmacological therapies
  - How effective and well-tolerated are the treatments, level and quality of evidence
- **Benefit**
  - Describe the trials (including strengths and weaknesses) , consistent w/ guidances?
  - What endpoints were evaluated? Clinically meaningful? Magnitude of benefit? Dose response studied? Subpopulation results
- **Risk**
  - Characterize the safety concerns in the trials. Incidence? Sub-population results? Is there a range in risk severity? Changes with continued exposure? Reversible?
  - Safety concerns from non-clinical data?
  - How might the incidence change in the post-market setting? Additional work needed to further characterize the risk?
- **Risk Management**
  - Which risks require mitigation or further characterization? What tools are recommended to address the risks?
  - What would constitute a successful plan? How measured? What is the burden on stakeholders?
  - Do you expect the tools to be effective in risk reduction?

Ruxolitinib Summary Review for Regulatory Action: From FDA CDER, Nov 2011 (1 of 2)

First therapeutic agent that decreases splenomegaly and ameliorates symptoms in primary or secondary myelofibrosis

Benefit-Risk Assessment Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition: MF Clinical Manifestations Median Survival (all groups) Survival high risk Survival intermediate-2 Approved available therapy	 Splenomegaly and symptoms which disrupt quality of life 57 months 27 months 48 months No approved therapy	MF is a serious, life-threatening condition in which death is due to evolution into AML (12%), bleeding (11%), portal hypertension (7%), and liver insufficiency (9%).
Unmet Medical Need: Therapy: Off label use of interferon-alpha, anagrelide, dexamethasone, hydroxyurea, erythropoietin, thalidomide, splenic radiation, and allografts.	Allograft is the only curative therapy (7-year survival is 60%). Only a fraction of patients with MF are eligible. All other therapies are palliative and have significant side effects.	For most patients, there is no curative therapy, and no effective treatment which reduces symptoms and splenomegaly for a long time. There is an unmet medical need in MF.
Clinical Benefit: 2 randomized, well controlled trials were conducted with reproducible results.	42% and 29% of ruxolitinib treated patients in the two trials displayed ≥35% reduction of splenic volume. In the pivotal phase III trial, 46% of patients experienced ≥50% reduction in total symptom score. Long term benefit and toxicity unknown.	Two large well controlled and well designed trials met efficacy endpoints when measured at 24 and 48 weeks of therapy. Uncertain is the how long benefits will last beyond the 24 and 48 weeks and what will be the toxicity of long-term treatment.
Risks: Early deaths (≤28 days) SAEs AEs ↓platelets (Grade 3) ↓platelets (no Grade 4) Bleeding	Ruxolitinib Arms Not increased Not increased Increased Not increased Not increased	Thrombocytopenia was successfully managed by a dose adjustment schedule. Anemia was managed by RBC transfusions. The risks of long term therapy have not been characterized.

Ruxolitinib Summary Review for Regulatory Action: From FDA CDER, Nov 2011 (2 of 2)

First therapeutic agent that decreases splenomegaly and ameliorates symptoms in primary or secondary myelofibrosis

Anemia (Grade 3) Anemia (Grade 4) Infections AEs leading to discontinuation AEs leading to dose reduction	Increased Increased Not increased Not increased Increased	
Risk Management: Need of studies for toxicity of long-term therapy.	Two phase III trials showed significant benefit and minimal risks for up to 48 weeks of treatment. Need PMC for longer term follow-up of response duration and toxicity.	PMR for follow-up (for 3 years after randomization) of phase III trial populations for myelosuppression PMC for post-marketing follow-up of efficacy and safety outcomes of current randomized trials and to report on discontinuation of at least 150 patients previously entered onto the randomized trials to determine if specific cautions are appropriate to describe discontinuation strategies.

Final Benefit-Risk Summary and Assessment: Two well designed, well controlled, randomized trials of ruxolitinib in patients with MF, who for the most part had no other available therapy, showed that clinically significant benefit was generated by ruxolitinib, and that the major side effect (thrombocytopenia) could be limited by dose adjustments which did not prevent the benefit otherwise generated by ruxolitinib.

Agenda

- **FDA Benefit-risk Framework**
- **BRAT Framework**

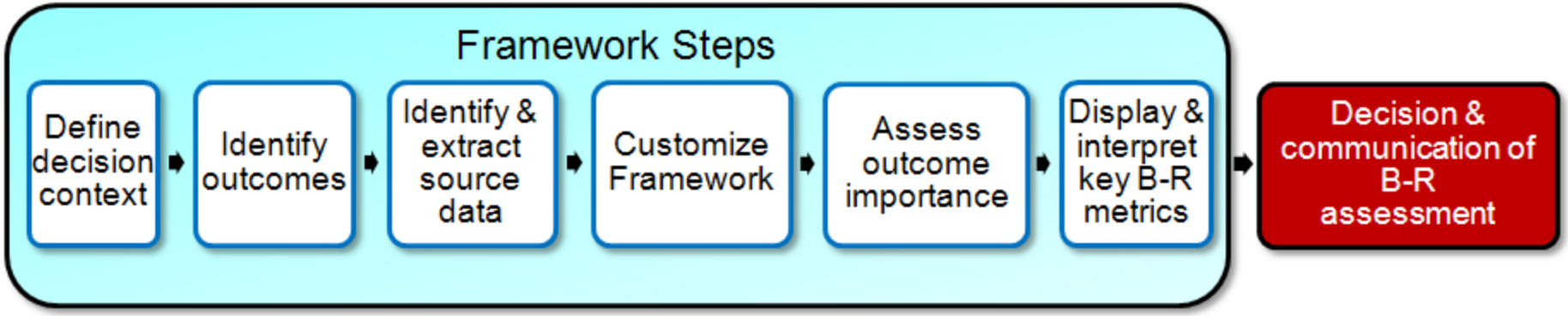
PhRMA Benefit Risk Action Team (BRAT)

- **Birth of BRAT**
  - BRAT started by PhRMA in 2006 in response to IOM and CHMP statements on benefit-risk (B-R) indicating the need to improve methodology, transparency, consistency and communication
- **BRAT Strategic Goals**
  - Increase transparency, predictability and consistency of B-R
  - Strengthen drug development and regulatory approval process
  - Improve communication of B-R information to patients and healthcare professionals
- **BRAT Tactical focus**
  - Develop a structured, transparent framework for B-R
  - Facilitate its use by pharmaceutical companies
  - Facilitate its integration into regulatory decision-making

PhRMA Benefit Risk Action Team (BRAT) Framework

- **A set of processes and tools to guide decision-makers in**
  - Selecting
  - Organizing
  - Analyzing
  - Communicating

  Evidence relevant to benefit-risk decisions



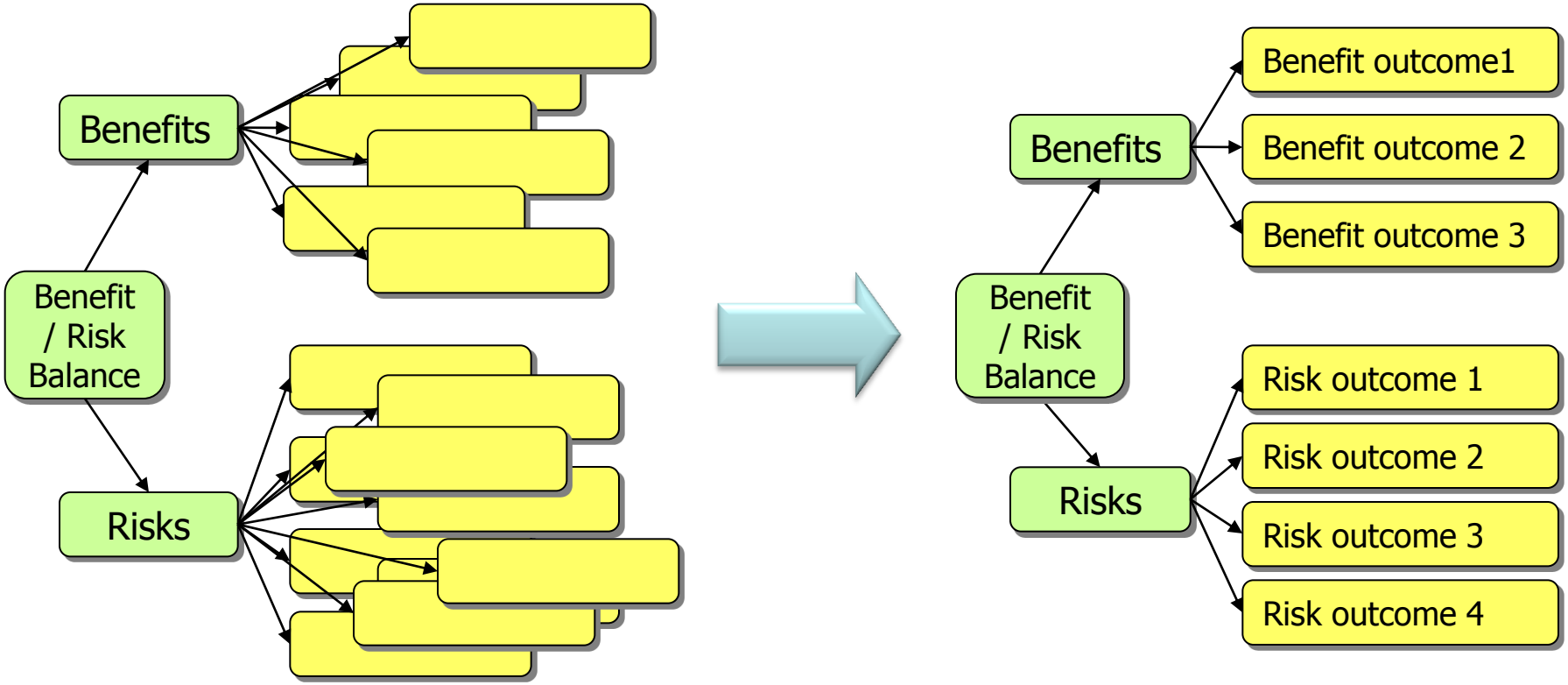
Steps in the BRAT Framework

Detailed User's Guide behind the steps

Step	Description
1. Define the decision context	• Define drug, dose, formulation, indication, patient population, comparator(s), time horizon for outcomes, perspective of the decision-makers (regulator, sponsor, patient, or physician)
2. Identify outcomes	• Select all important outcomes and create the initial value tree. • Define a preliminary set of outcome measures/endpoints for each. • Document rationale for outcomes included/excluded
3. Identify and extract source data	• Determine and document all data sources (e.g., clinical trials, observational studies) • Extract all relevant data into the data source table, including detailed references and any annotations to help the subsequent interpretations
4. Customize the framework	• Modify the value tree based on further review of the data and clinical expertise • Refine the outcome measures/endpoints • May include tuning of outcomes not considered relevant to a particular benefit-risk assessment or that vary in relevance by stakeholder groups
5. Assess outcome importance	• Apply or assess any ranking or weighting of outcome importance to decision-makers or other stakeholders
6. Display and interpret key benefit-risk metrics	• Summarize source data into tabular and graphical displays to aid interpretation • Challenge summary metrics, review source data, identify and fill any information gaps • Interpret summary information

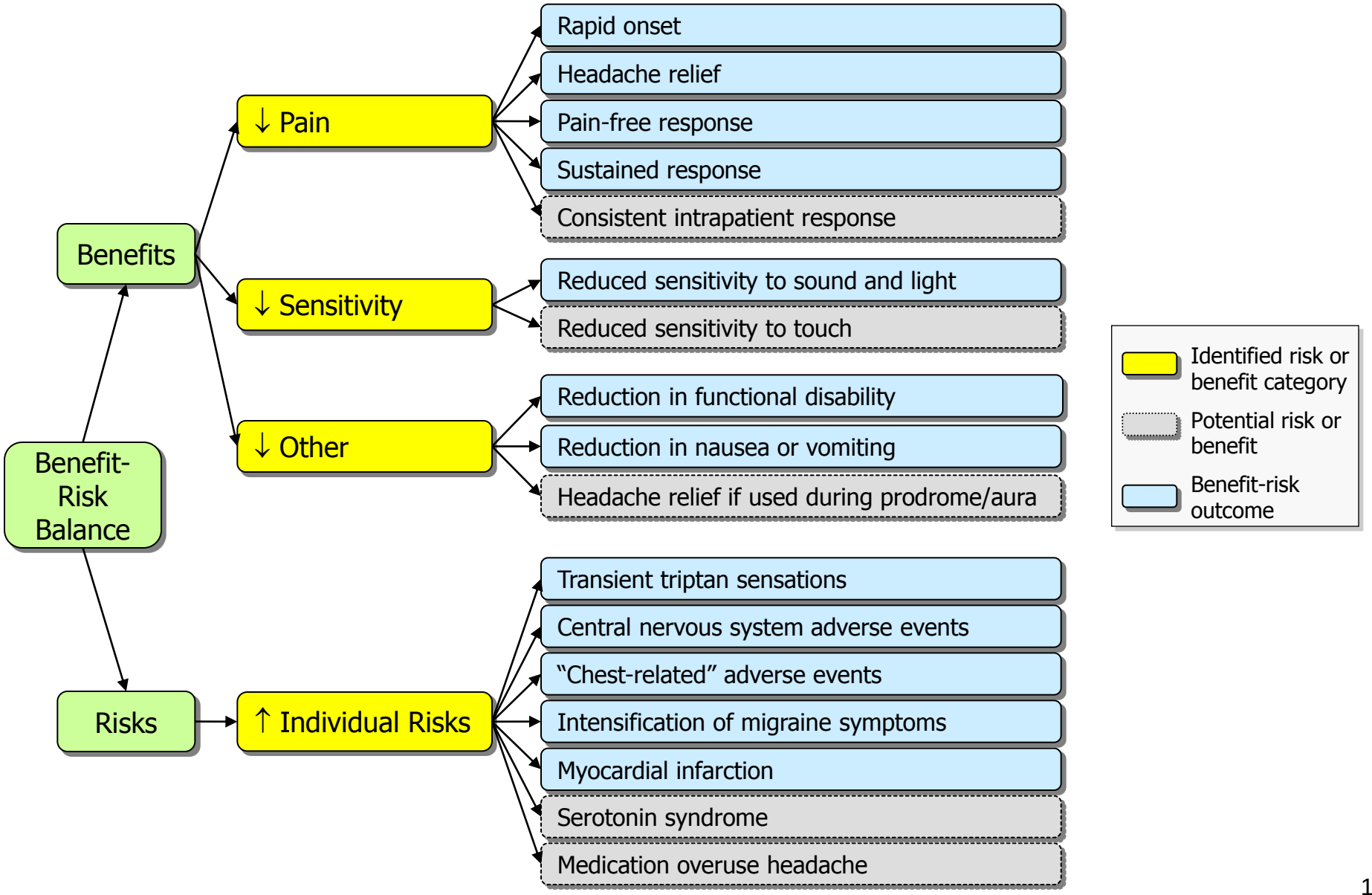
Framework Process – Value Tree

Establish a preliminary scope for the benefit-risk assessment by identifying and paring down potential benefit/risk outcomes



Framework can serve as basis for discussion with health authorities to prospectively frame the benefit-risk assessment

Value Tree for PhRMA BRAT Triptans Example

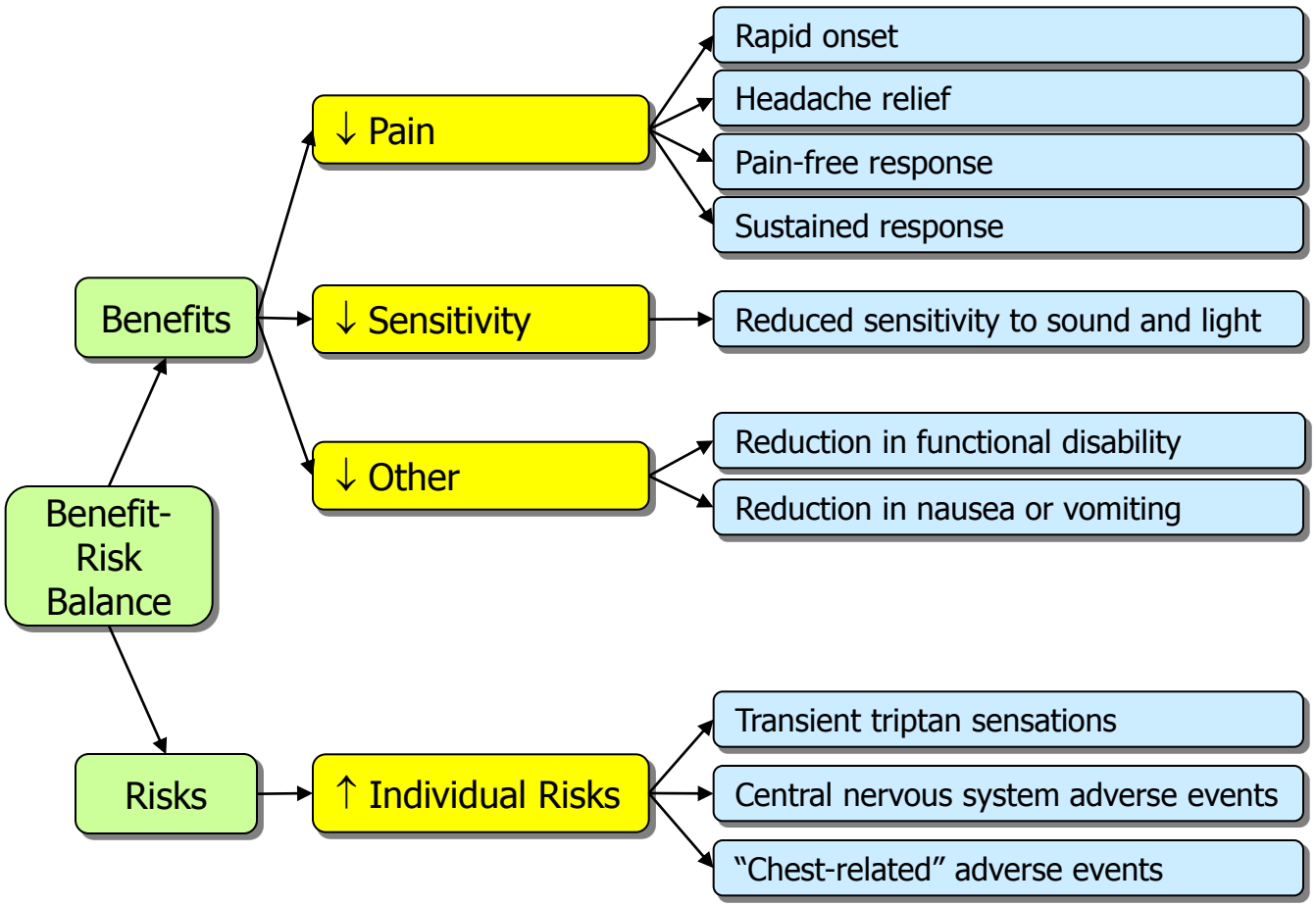


Definitions of Endpoints for each Outcome

Outcome	Endpoint Definition
Rapid onset	Proportion of patients (pts.) with moderate/severe headaches that improve to no/mild pain 1 hour after dosing
Headache relief	Proportion of pts. with severe/mild headaches that improve to mild/no pain by 2 hours after dosing
Pain-free response	Proportion of pts. with moderate/severe headaches that improve to no pain 2 hours after dosing
Sustained response	Proportion of pts. pain free at 2 hours with no recurrence of pain by 24 hours after dosing (use of NSAIDs and other non-triptans/non-ergotamines allowed)
…	…
Transient triptan sensations	Proportion of pts. with flushing, warm sensation in limbs, or paresthesias within 2 hours of dosing
CNS AEs	Proportion of pts. reporting asthenia, agitation, ataxia, aphasia, confusion, tremor, vertigo, etc.
…	…

Value Tree for PhRMA BRAT Triptans Example

Tuning the tree helps simplify the assessment, temporarily simplifying the display to focus on the more critical outcomes



Identified risk or benefit category

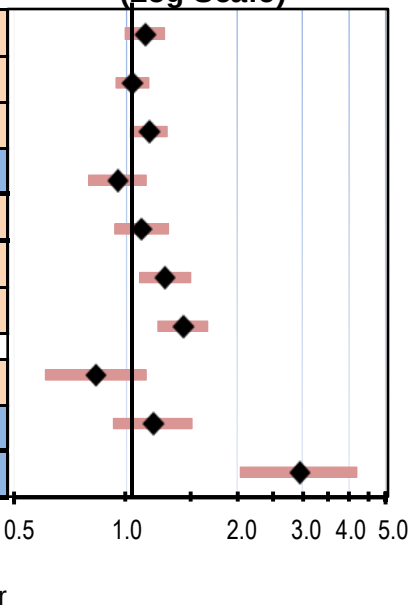
Benefit-risk outcome

Documented rationale for any outcomes tuned from the display

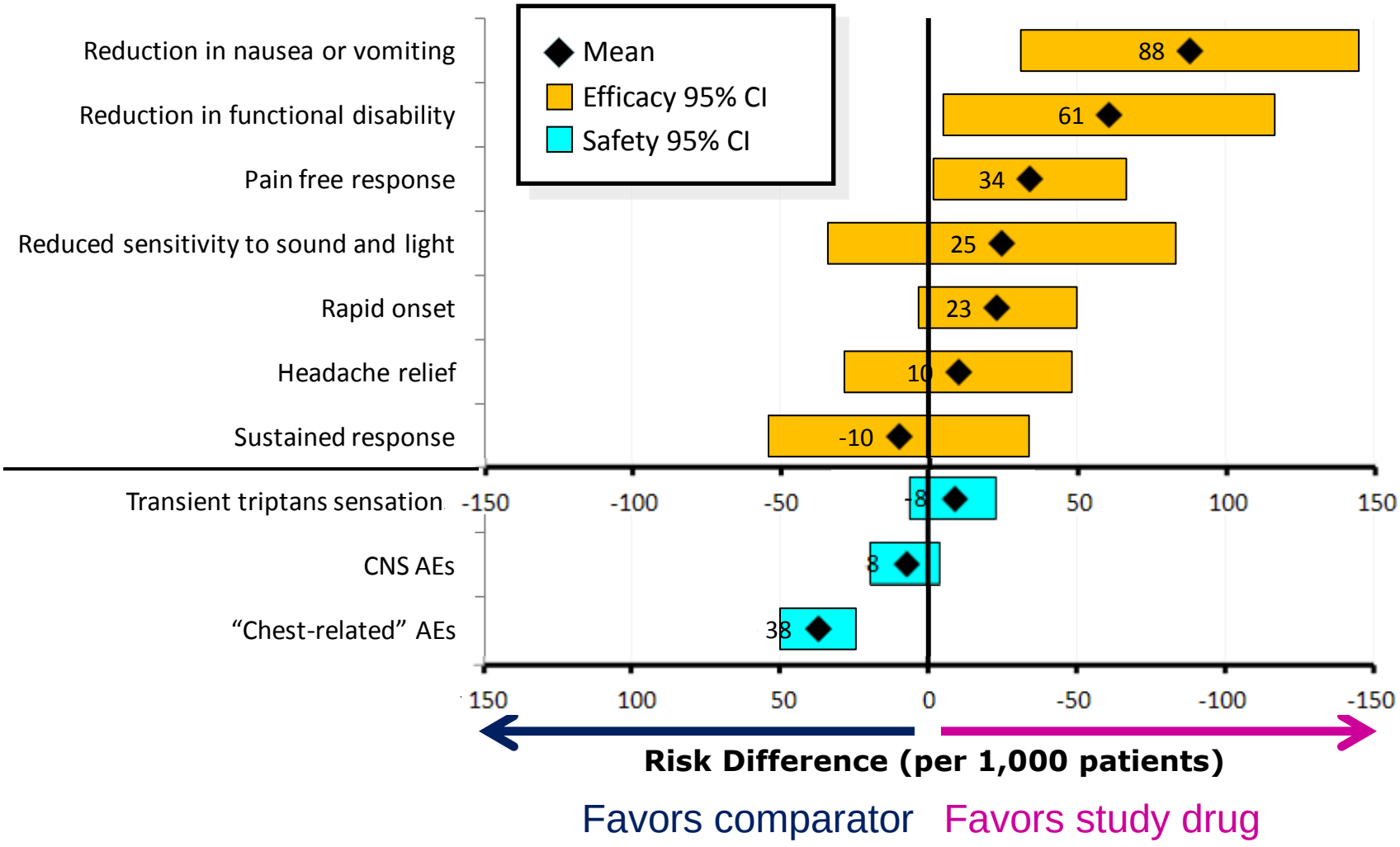
BRAT Framework Key Benefit-Risk Summary Table

- **Top-level representation of information in the framework**
- **The most critical view that decision makers will have on the data**
- **Use of graphic or tabular displays as needed to support rapid interpretation of information on multiple outcomes**

		Outcome	Study Drug Risk (/1,000 pts)	Comparator Risk (/1,000 pts)	Odds Ratio (95% CI)
Benefits	↓ Pain	Rapid onset	271	248	1.13 (1.00,1.27)
		Headache relief	643	633	1.04 (0.94,1.15)
		Pain free response	383	349	1.16 (1.03,1.30)
		Sustained response	285	295	0.95 (0.80,1.14)
	↓ Sensitivity	Reduced sensitivity to sound and light	530	505	1.10 (0.94,1.30)
	↓ Other	Reduction in functional disability	540	480	1.28 (1.09,1.49)
		Reduction in nausea or vomiting	604	517	1.43 (1.22,1.67)
Risks	↑ Individual Risks	Transient triptans sensations	43	52	0.83 (0.61,1.14)
		CNS AEs	53	45	1.18 (0.92,1.51)
		"Chest-related" AEs	58	21	2.93 (2.04,4.20)



BRAT Graphical Display: Risk Difference Forest Plot



References on Regulatory and Industry Initiatives on Structured Approaches to B-R

- **FDA**
  - http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm
  - http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf
- **EMA**
  - http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000314.jsp&mid=WC0b01ac0580665b63
  - http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004800.pdf
  - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC500123207.pdf
- **CIRS**
  - http://cirsci.org/UMBRA
- **IMI PROTECT**
  - http://www.imi-protect.eu/benefitsRep.shtml
- **BRAT**
  - Coplan, Noel, Levitan, et. al. (2011) Clin Pharmacol Ther, 89:312-315
  - Levitan, Andrews, Gilsenan, et al. (2011). Clin Pharmacol Ther, 89:217-224
  - Noel, Herman, Levitan, et al. (2012). Drug Inf Jour 2012;46(6):736-743

Pragmatic Considerations for Endpoint Selection and Display in Cardiovascular Benefit-Risk Assessment

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What Approaches are Available to Set up a Benefit-risk Assessment?

- **Often numerous ways to set up an assessment**
- **Vary considerably in their flexibility, expertise needed, applicability, ease of communication, etc.**
- **Will share insights on setting up cardiovascular benefit-risk assessment from personal experience using**
  - Mock vignettes
  - Data from anticoagulant rivaroxaban used in FDA advisory committee meetings

Agenda

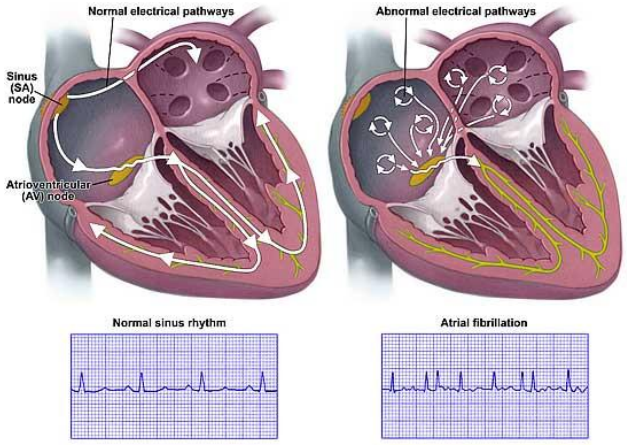
- **Efficacy Endpoints + Safety Endpoints ≠ Benefit-risk Endpoints**

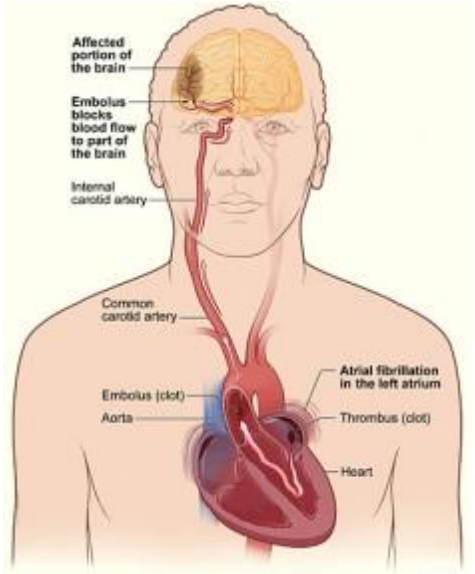
- **Approaches for Benefit-risk Endpoint Selection and Display in Cardiovascular Studies**

Atrial Fibrillation Example: Background

Atrial Fibrillation

- **Irregular, rapid heart rate due to poor conduction of electrical signals in the heart → impacts blood flow**
- **Generally not life-threatening, episodic or chronic**
- **Common (>2.3 million in US, >6% for those >80 years of age)**
- **Well established association with increased stroke risk**





http://www.saintvincenthealth.com/Services/Heart/Heart-Resource-Library/Atrial-Fibrillation/default.aspx

http://kardiol.com/?p=389

Atrial Fibrillation Example: Treatment and Medical Need

- **Anticoagulant prophylaxis (ex: vitamin K antagonists - VKAs) lowers stroke risk.**
- **However, many patients do not receive effective or optimal management due to**
  - Concerns about bleeding
  - Regular monitoring of clotting time (INR)
  - Food interactions
  - Long onset/offset time
- **Variety of new oral anticoagulants approved in the last few years**

Generic Clinical Study for Atrial Fibrillation

- **Study drug:** **Anticoagulant**
- **Comparator:** **Standard of care**
- **Population:** **Adults w/ AFib**

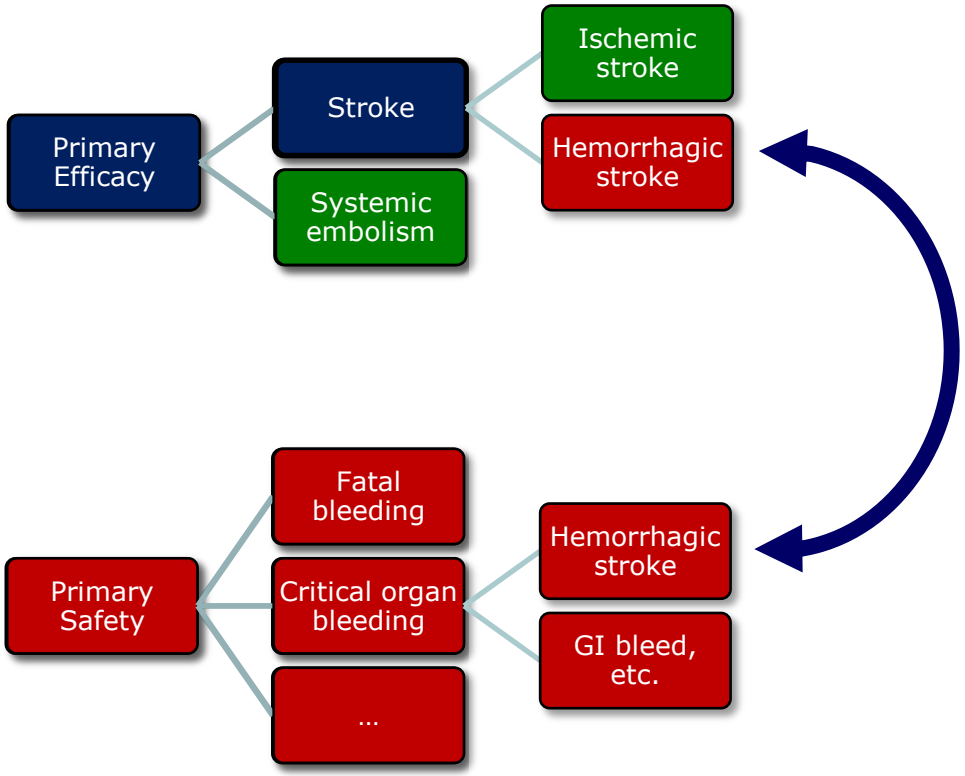
- **Standard endpoints in statistical analysis plan:**
  - Primary efficacy: Stroke or non-CNS systemic embolism
  - Primary safety: ISTH* Major bleeding; i.e.,
    - Fatal bleeding
    - Symptomatic bleeding in critical area/organ (ex: ICH, GI bleeding)
    - Transfusion (≥ 2 units)
    - Reduction in hemoglobin (≥2 g/dL)

* International Society on Thrombosis and Haemostasis

Can These Efficacy and Safety Endpoints Be Used for Benefit-risk Assessment?

- **Endpoints are fine for efficacy and safety considered independently**
- **Considered together, these primary endpoints may be problematic for B-R**
- **Potential challenges:**
  - Double-counting
  - Mismatched populations and time periods
  - Mixing of events with a wide range of clinical impact

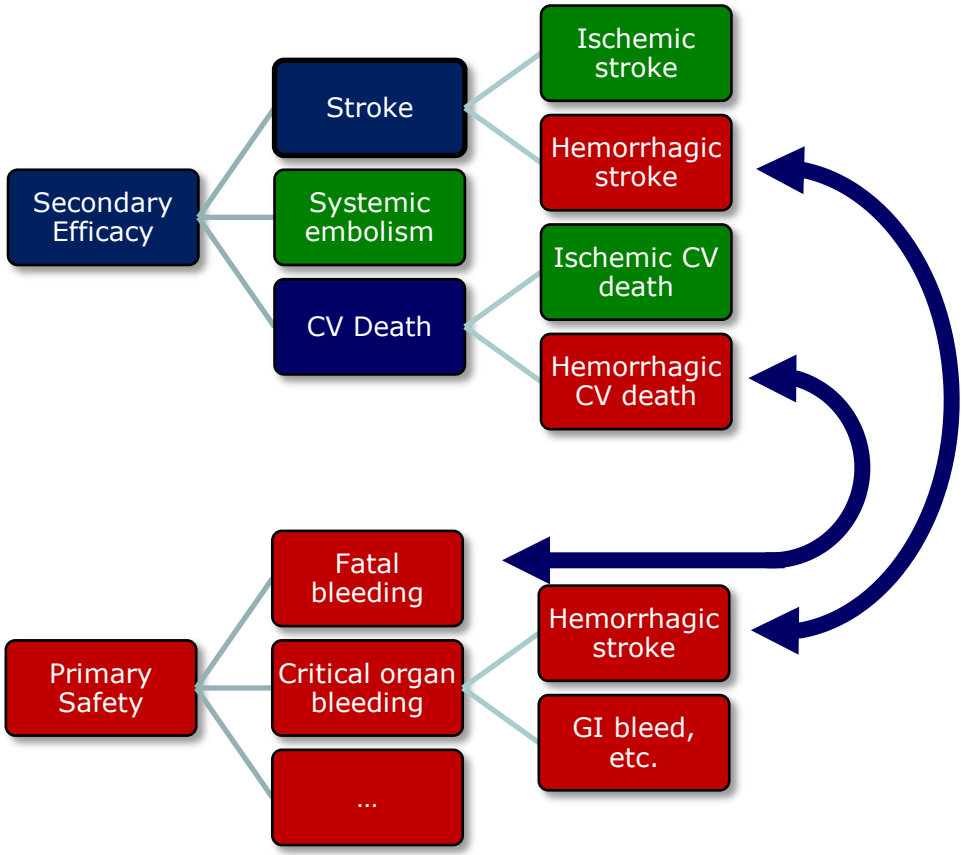
Double-counting of Events



- Events are double-counted
- Comparison of primary endpoints can be misleading
- Can not clearly compare benefits gained vs. harms caused

Ischemic events
Hemorrhagic events
Mixed events

Even More Double-Counting With a Typical Secondary Efficacy Endpoint for Atrial Fib



- Events are double-counted
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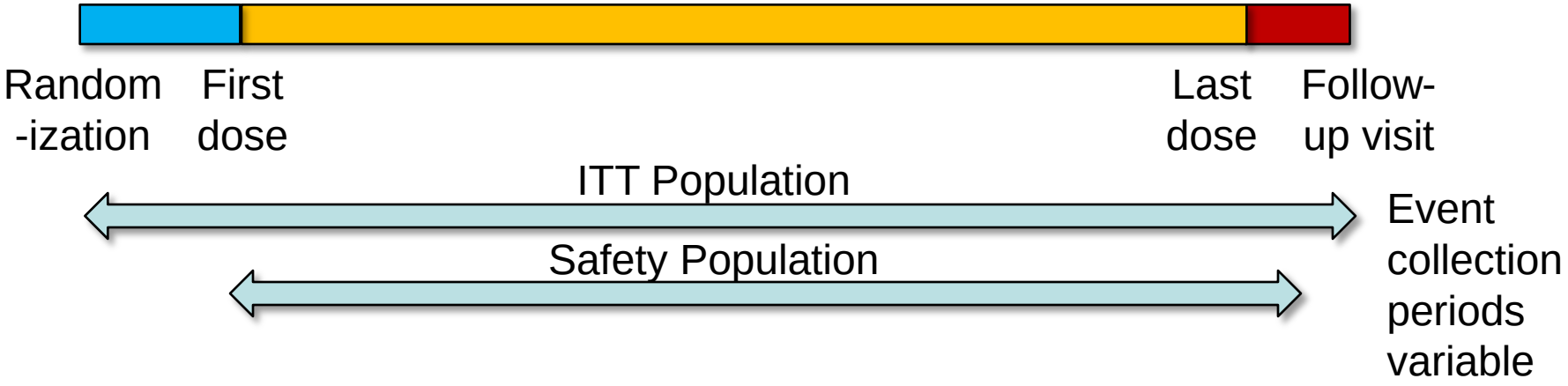
Ischemic events
Hemorrhagic events
Mixed events

Mismatched Populations and Time Periods

Typical randomized clinical trial timeline:



- **Efficacy endpoints typically assessed in Intention To Treat (ITT) population**
- **Safety endpoints typically assessed in Safety Population**
- **Can result in misleading comparison**

Mixing of Events with Large Differences in Clinical Impact

- **ISTH Major bleeding:**
  - Fatal bleeding
  - Symptomatic bleeding in critical area/organ
  - Transfusion (≥ 2 units)
  - Reduction in hemoglobin (≥2 g/dL)
- **Impact ranges from death and disabling bleeding only requiring supportive care**

- **Using major bleeding as a whole for B-R decisions can be misleading depending on which events predominate***
  - FDA decisions for prasugrel and dabigatran stressed the importance of considering fatal/irreversible harm events separately**

* Kaul and Diamond, J Am Col Cardiol. 2010 (55)

** Unger, NEJM 2009 (361); Beasley, Unger and Temple, NEJM , 2011 (364)

Agenda

- **Efficacy Endpoints + Safety Endpoints ≠ Benefit-risk Endpoints**
- **Approaches for Benefit-risk Endpoint Selection and Display in Cardiovascular Studies**

Three Approaches to Endpoint Selection in Cardiovascular Benefit-risk

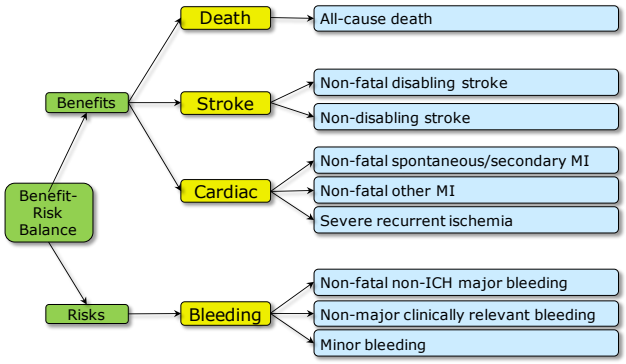
- **Composite net clinical outcome (NCO) endpoints**
  - Include both efficacy and safety events within a single composite endpoint

NCO

- **Pairwise comparisons**
  - Compare an efficacy endpoint to a safety endpoint

Efficacy vs. Safety

- **Full value tree/full set of benefits and harms**
  - Include all key benefits and harms individually



Composite Net Clinical Outcome Endpoints

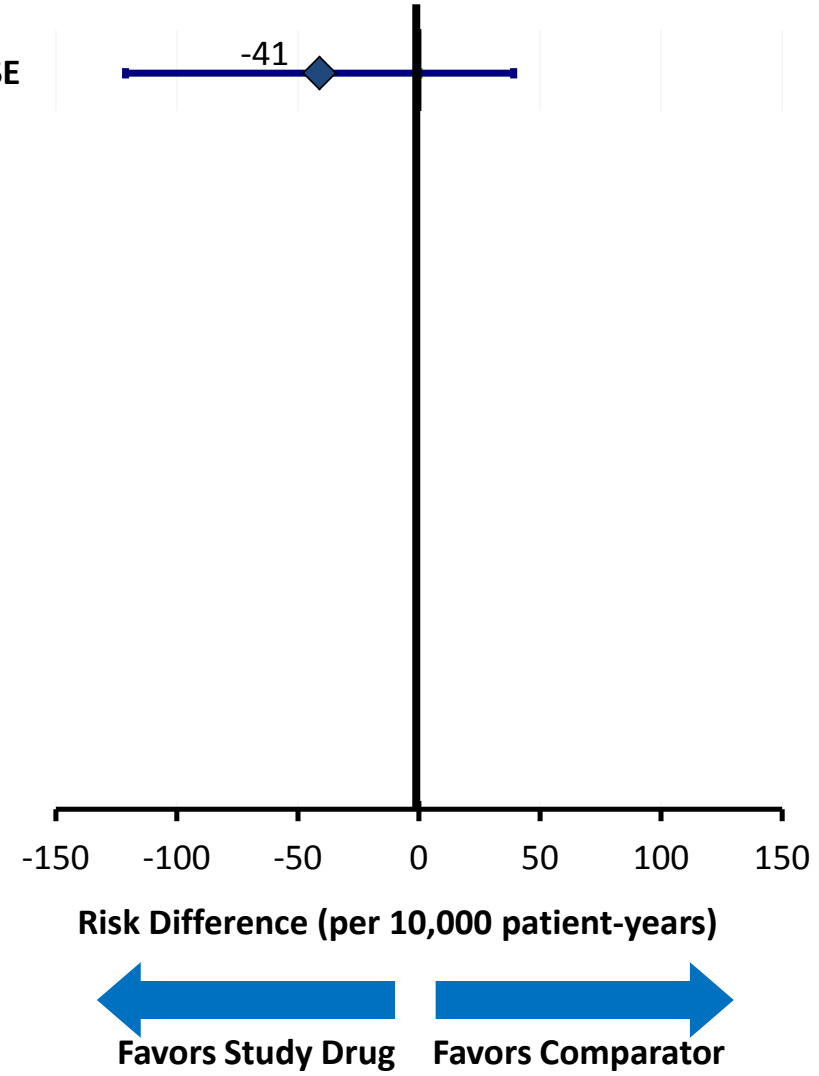
- **Endpoint that includes both efficacy and safety events within a single composite**
  - Ex: death + stroke + MI + major bleeding + non-CNS embolism
- **Pros:**
  - Conventional, simple measure, easy to understand
  - With time to first event or to most severe event approach, no events are double-counted
- **Cons:**
  - Each outcome is considered clinically equivalent
  - Hides impact of components (ex: What are the main drivers?)
  - Only counts one event per patient

➔ Can hide the efficacy/safety tradeoff and misrepresent the B-R balance

Composite NCO Endpoints Can Hide Tradeoffs (mock data)

- NCO (death, stroke, MI, major bleeding + NCSE) is not statistically significant

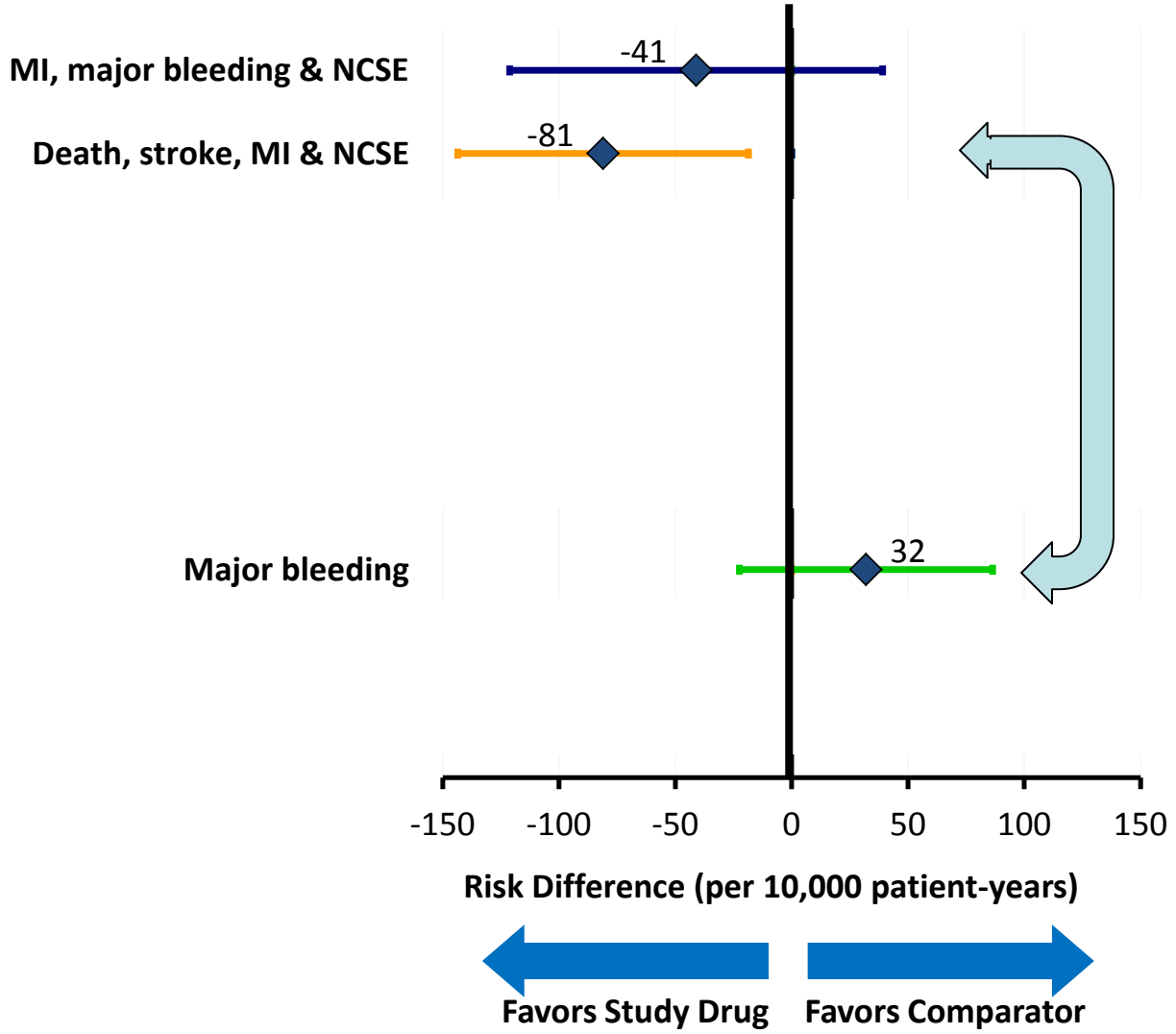
- Has benefit-risk failed?



NCSE = Non-CNS systemic embolism

Composite NCO Endpoints Can Hide Tradeoffs (mock data)

- Main driver for lack of significance is major bleeding
- Real tradeoff is between efficacy events and transfusions/Hgb decreases
- Composite NCO endpoint hides the real tradeoff



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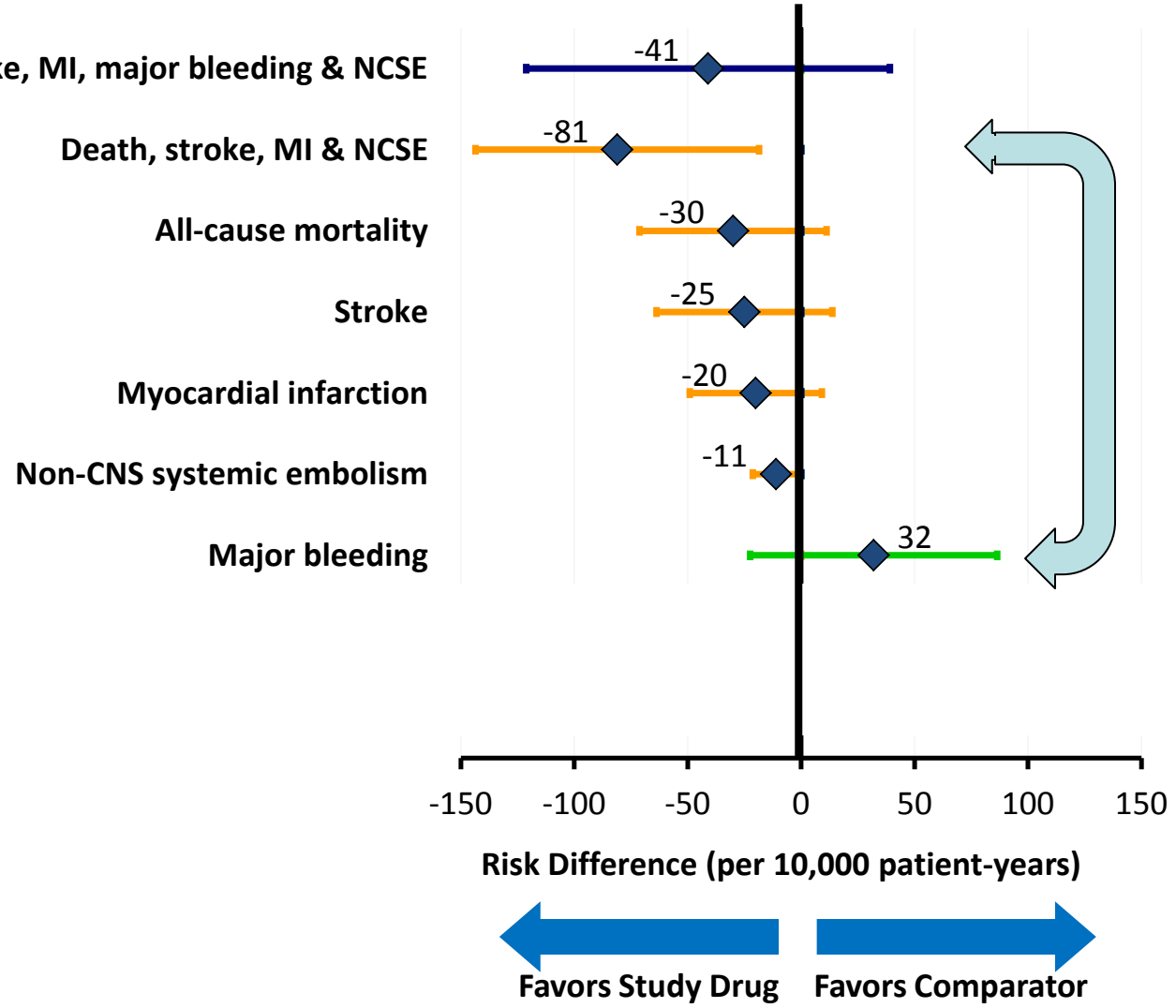

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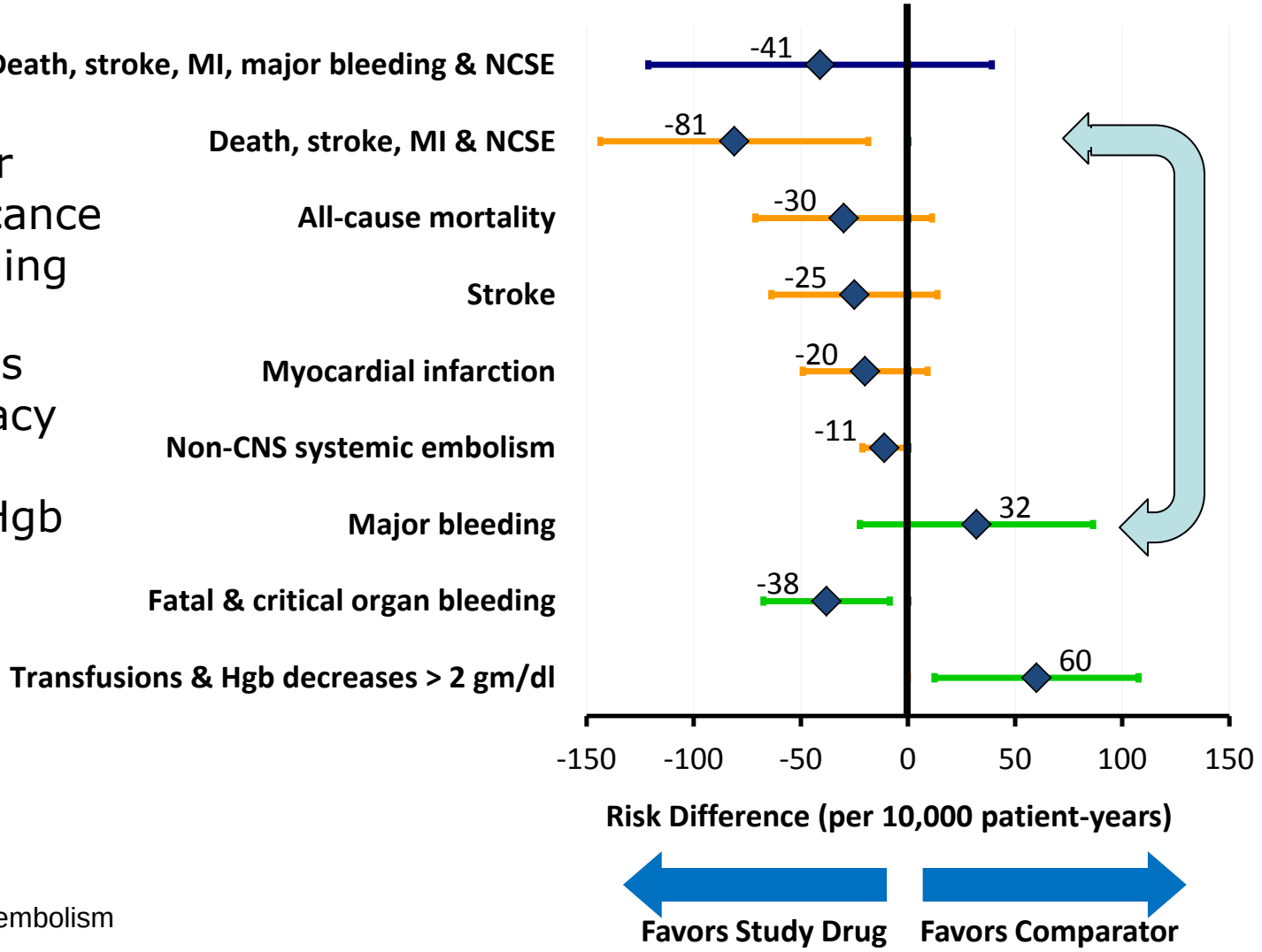


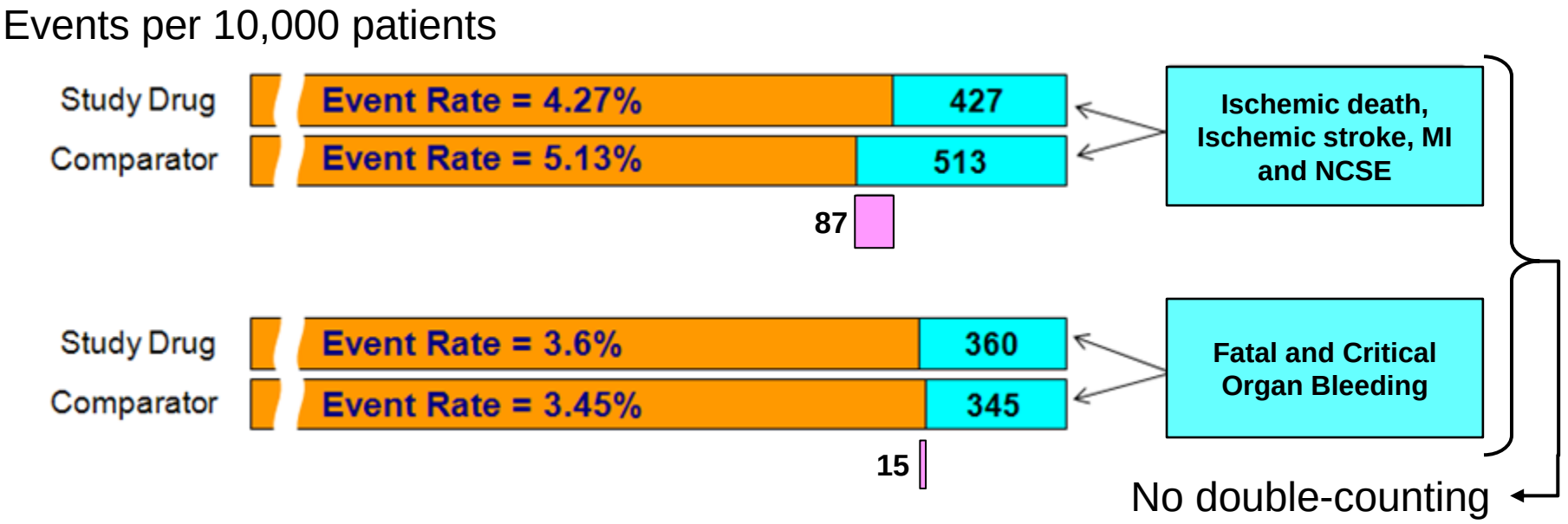
NCSE = Non-CNS systemic embolism

Pairwise Comparisons

- **Compares two endpoints**
  - Composite efficacy endpoint; composite safety endpoint
  - Ideally mutually exclusive
- **Pros:**
  - Easy to understand
  - Clear comparison between key efficacy and safety events
  - Simple application to NNT/NNH, B-R ratio, B-R over time, …
- **Cons:**
  - Treats separate events within each composite as clinically equivalent
  - May not be possible to define pairs of similar clinical impact
  - Can depart from SAP in ways that challenge development team

NNT = number needed to treat NNH = number needed to harm

Example Pairwise Comparison (mock data) Focusing on Fatal/Irreversible Events*



Multiple ways to interpret pairwise comparisons:

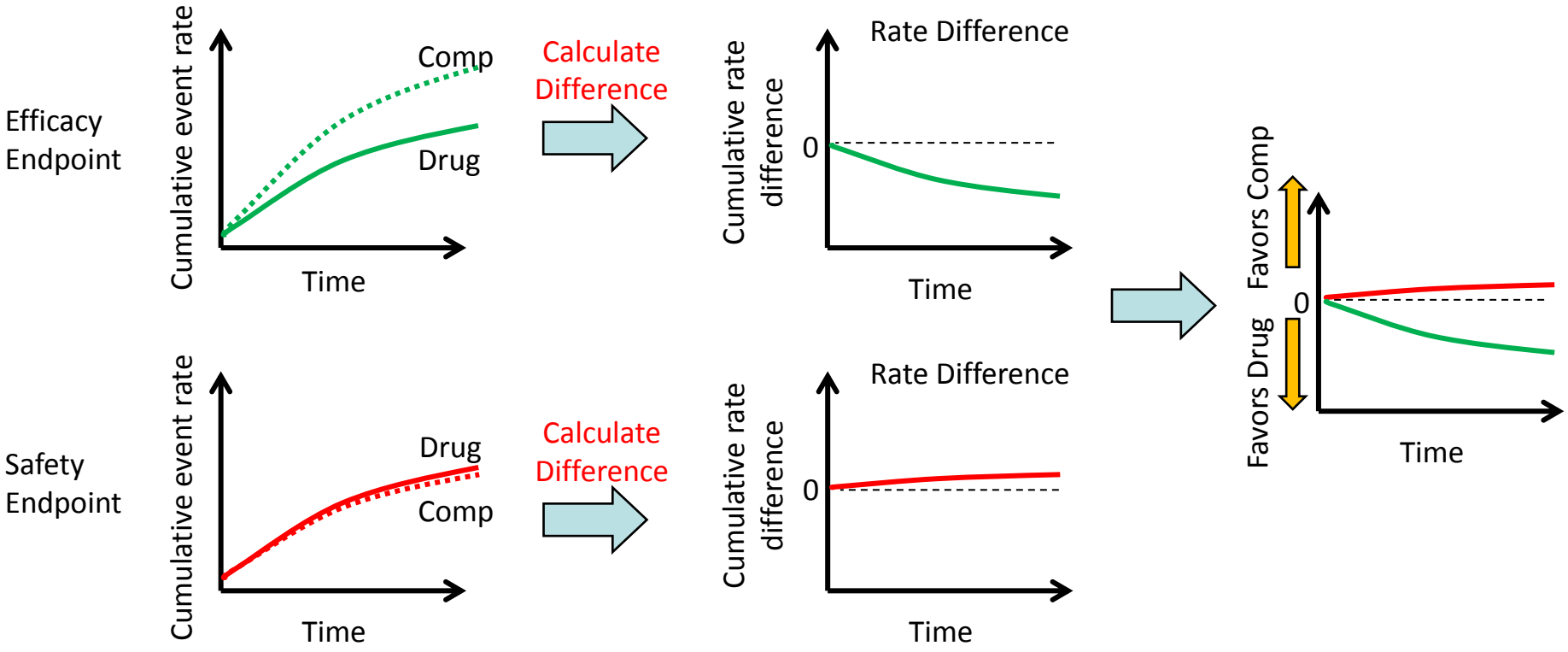
- 87 harmful events prevented vs. 15 caused / 10,000 patients
- NNT = 115; NNH = 714
- Ratio of ~6 (87/15) harmful events prevented to harmful events caused
- Net effect of 72 (95% CI -148 to 3) harmful events prevented overall

NCSE = Non-CNS systemic embolism

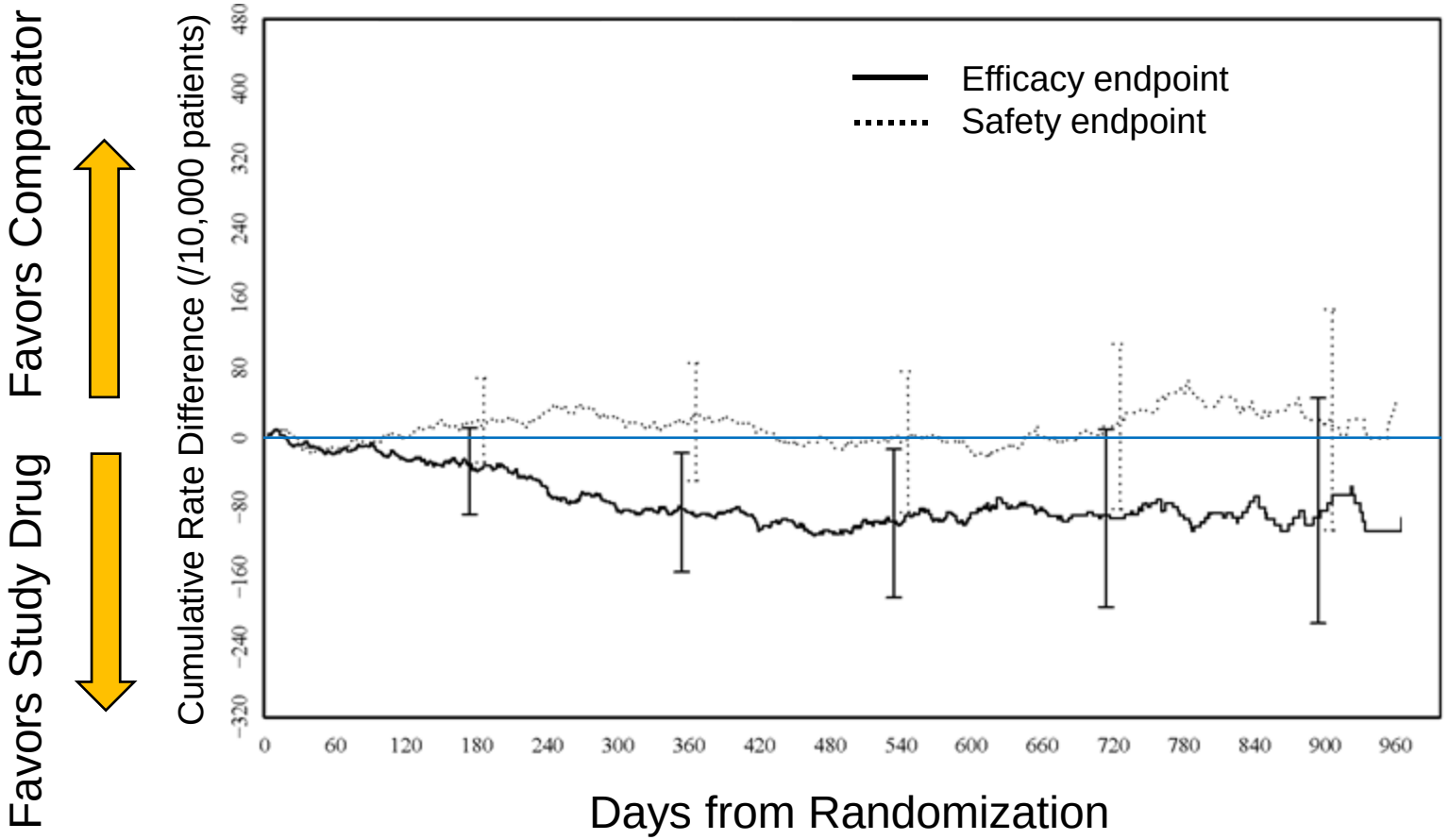
* Unger, NEJM 2009 (361); Beasley, Unger and Temple, NEJM , 2011 (364)

Can Assess Temporal Course of Benefit-Risk With Pairwise Comparisons

- **Convert Kaplan-Meier rates to rate differences over time**



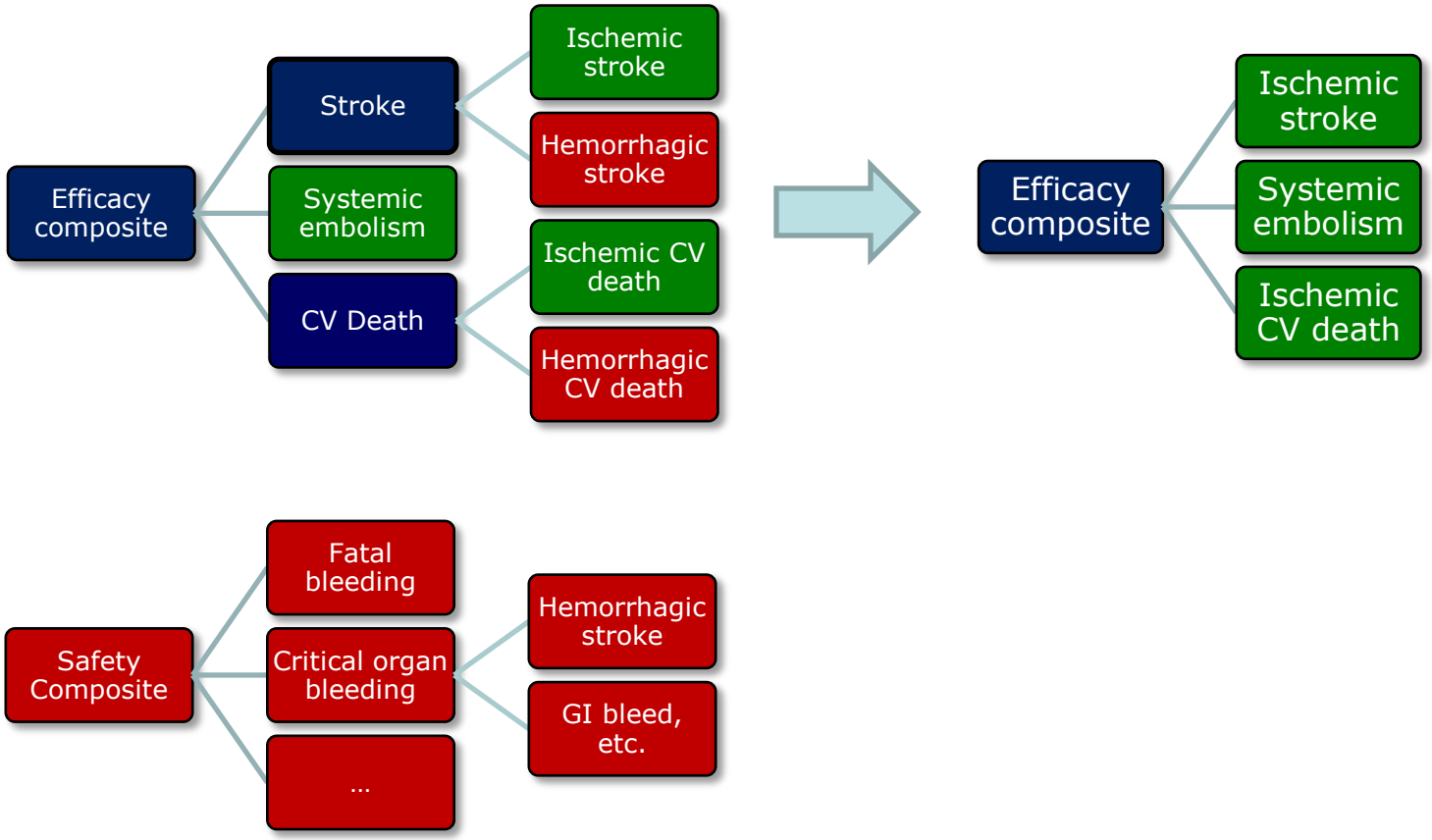
Temporal Course of Excess Number of Events for Efficacy Endpoint vs safety endpoint



Redefining Endpoints to Avoid Double-Counting

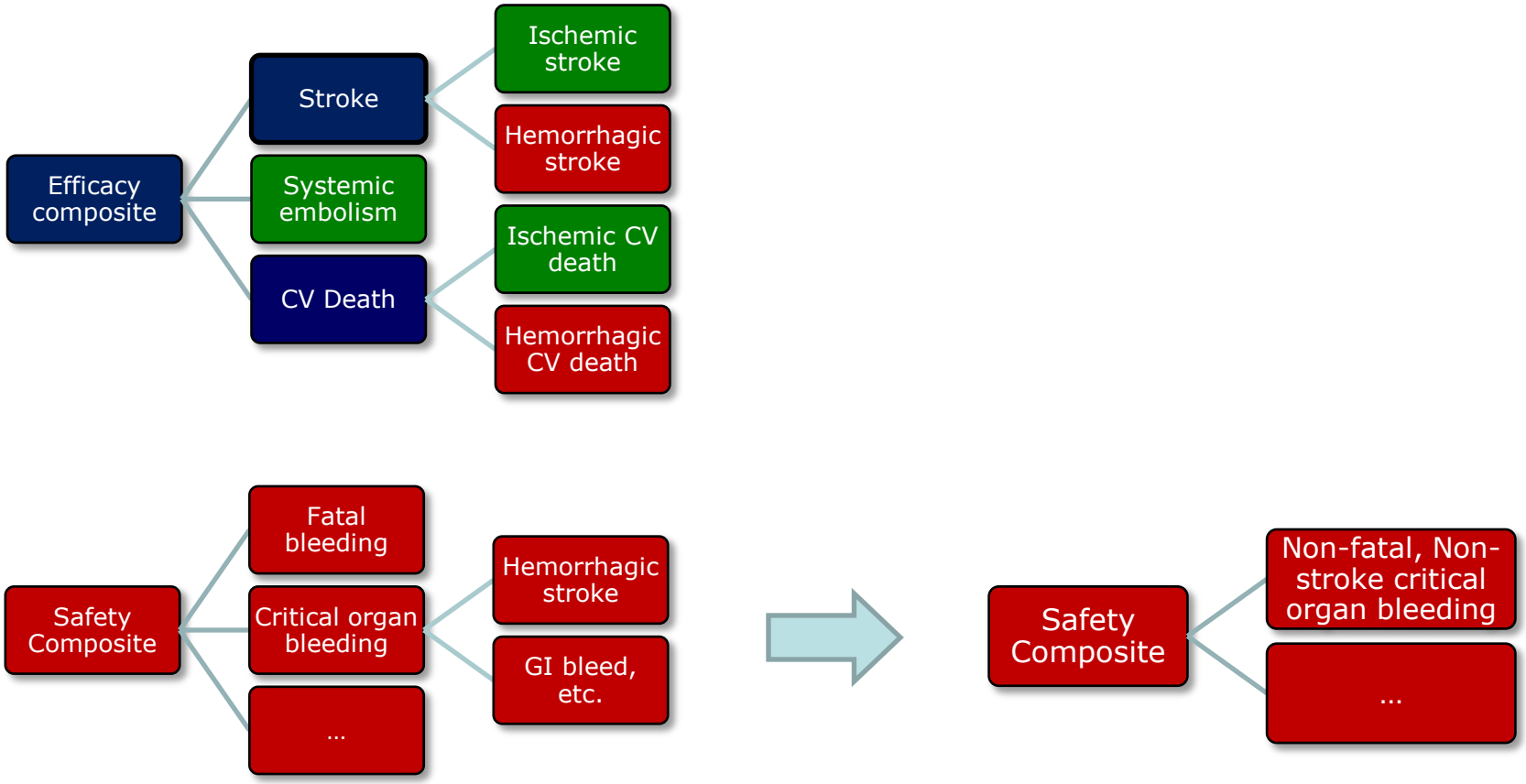
- **Not always as simple as it seems**
- **Usually two approaches**
- **Deviation from SAP can be problematic for clinical development team or reviewers**

One Approach: Remove Hemorrhagic Events From the Efficacy Composite



- Separates events prevented (ischemic) from events caused (hemorrhagic)
- Can be problematic due to modifying the primary efficacy endpoint from SAP and changing expectations

Second Approach: Remove Ischemic Events From the Safety Composite



- Preserves the prespecified primary efficacy endpoint
- But ischemic and hemorrhagic events mixed under the “efficacy” composite

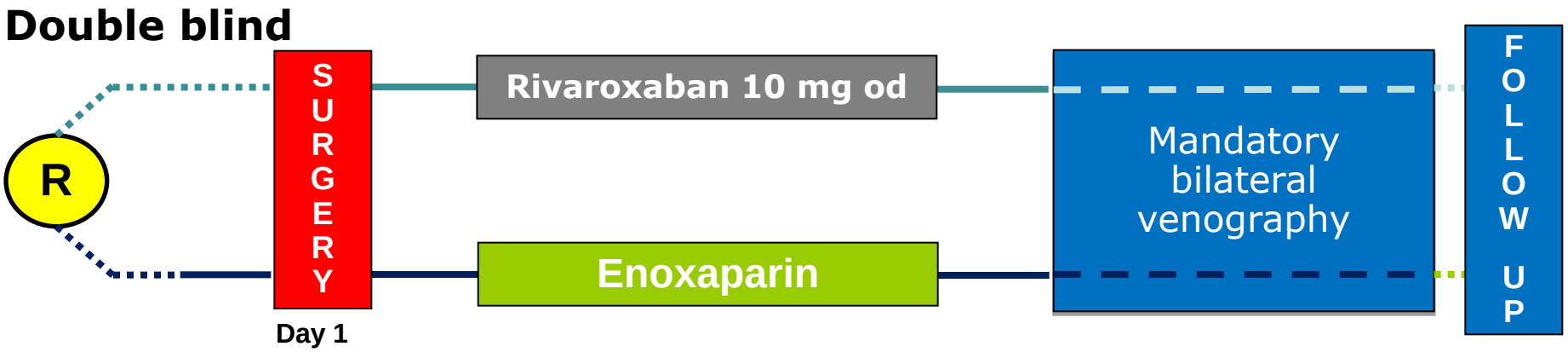
Rivaroxaban

Cardiovascular and Renal Drugs Advisory Committee
March 19, 2009

Rivaroxaban Benefit-Risk Assessment

- **Rivaroxaban is an oral direct factor Xa inhibitor**
  - Inhibits a step in the clotting cascade
  - Co-developed by Bayer HealthCare and J&J PRD
- **Prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing:**
  - Hip replacement surgery (>300,000 / year in US)
  - Knee replacement surgery (>500,000 / year in US)
  - Current prophylaxis – substantial benefits but risks and limitations
- **Advisory Committee Meeting March, 2009**
- **Goal was to demonstrate benefits in reducing symptomatic non-fatal DVTs, PEs and death exceeds bleeding risks**
- **Assessment by Bennett Levitan, Zhong Yuan and Jesse Berlin**

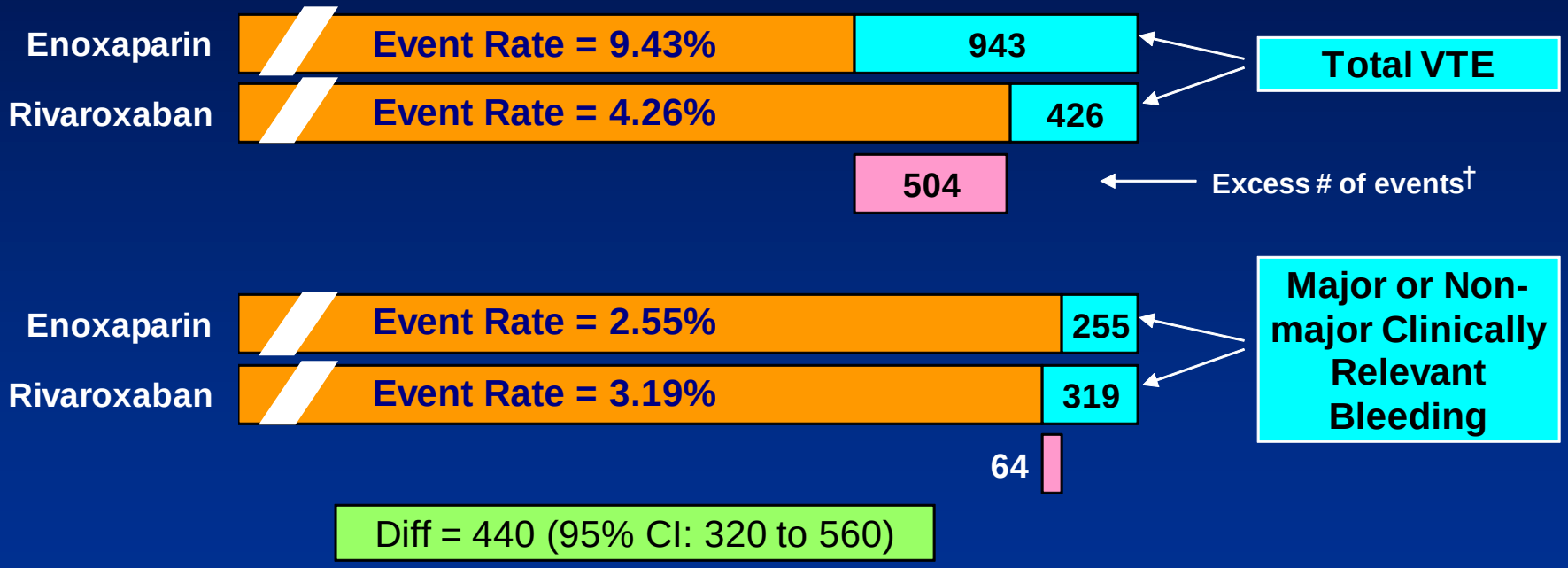
RECORD Phase III Program: Simplified Study Design



- **Four studies (RECORD1 – 4) compared rivaroxaban to enoxaparin for preventing DVTs and PEs after hip or knee replacement surgery**
  - Two hip replacement studies
  - Two knee replacement studies
- **Studies had same endpoints but differed in timing and doses + combination placebo/enox comparator in RECORD2**
- **12,729 patients randomized, results pooled over all 4 studies**

RECORD 1–4: Excess Number of Events
(Total VTE* vs. Major/Non-Major Clinically Relevant Bleeding)

Treating 10,000 patients in each group:

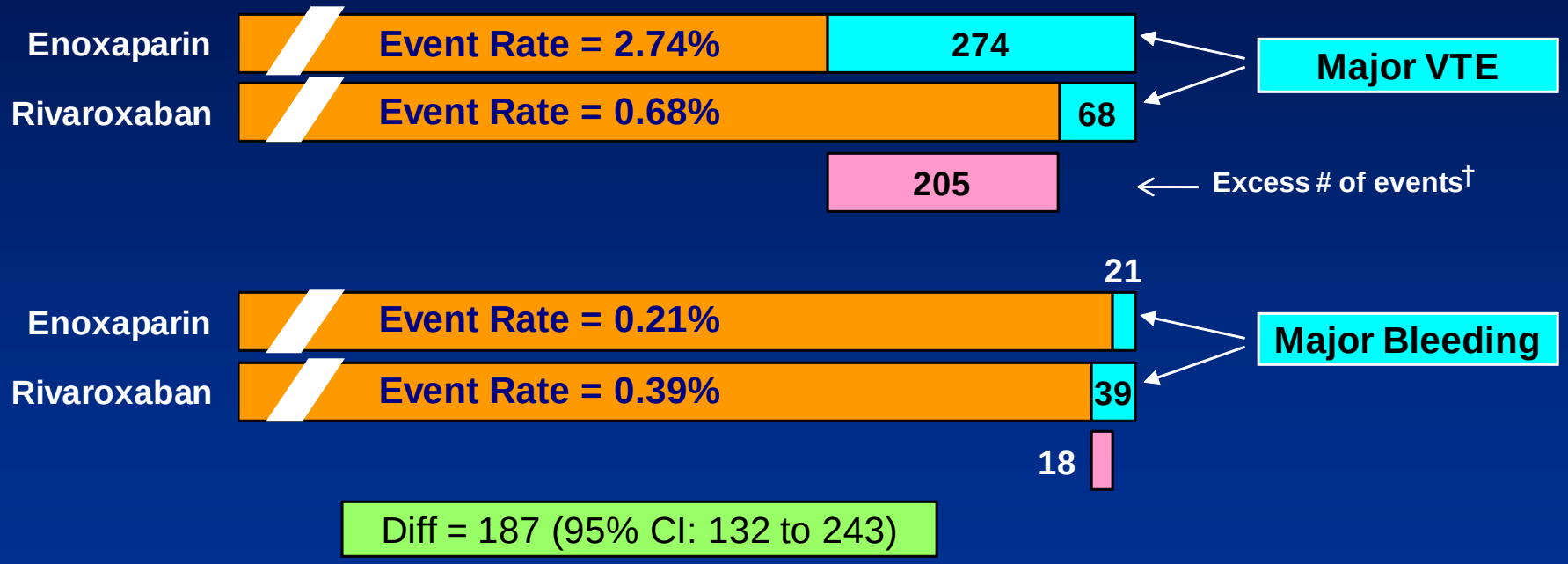


† Excess # of events is based on Mantel-Haenszel-weighted treatment difference and is not identical to crude rate difference.

* Total VTE was a prespecified primary efficacy endpoint in the individual RECORD studies and is based on the MITT population for Total VTE; Bleeding results from safety population.

RECORD 1–4: Excess Number of Events (Major VTE* vs. Major Bleeding)

Treating 10,000 patients in each group:

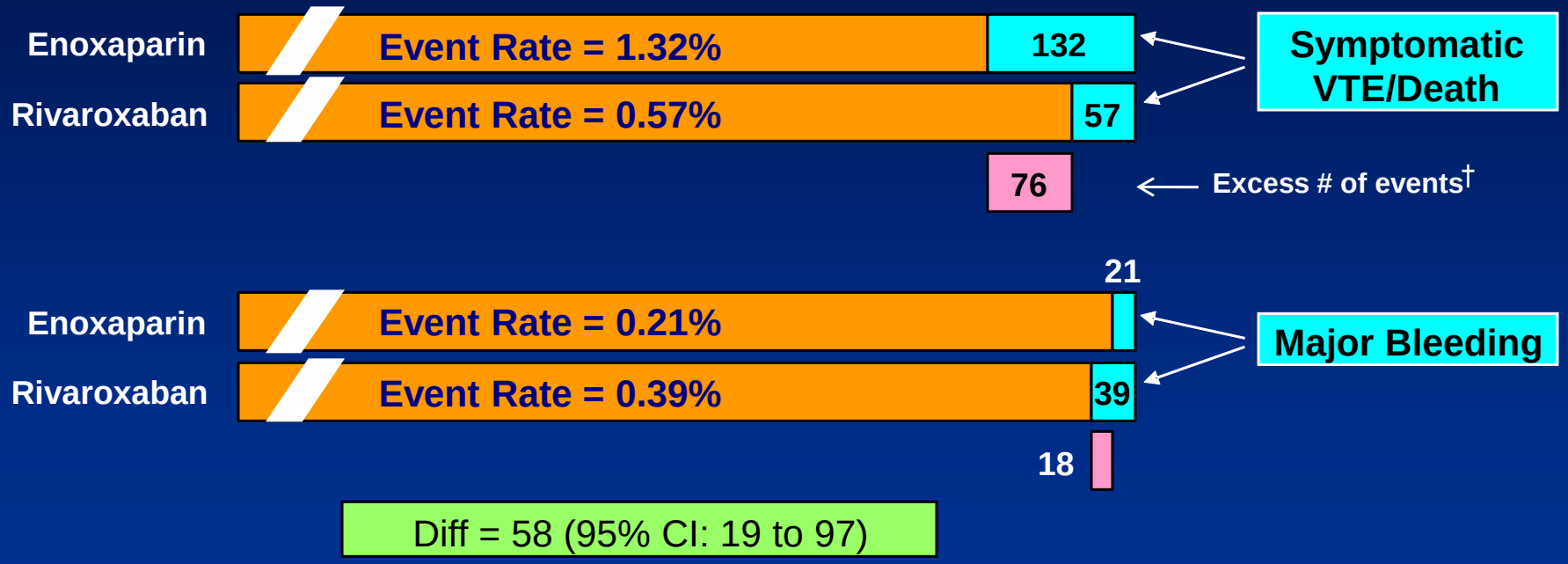


† Excess # of events is based on Mantel-Haenszel-weighted treatment difference and is not identical to crude rate difference.

* Major VTE was a prespecified secondary efficacy endpoint in the individual RECORD studies and is based on the MITT population for major VTE; Bleeding results from safety population.

RECORD1–4: Excess Number of Events (Symptomatic VTE/Death* vs. Major Bleeding)

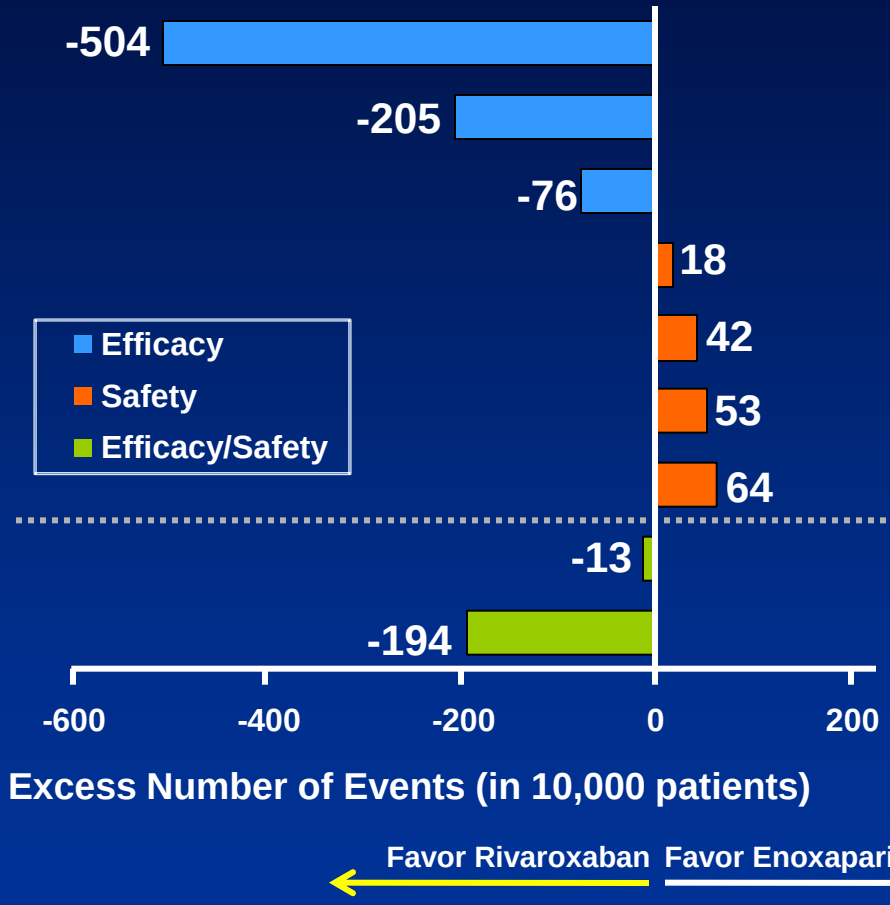
Treating 10,000 patients in each group:



† Excess # of events is based on Mantel-Haenszel-weighted treatment difference and is not identical to crude rate difference.

* Symptomatic VTE/death from all causes was the primary endpoint in pooled analysis of RECORD studies; Efficacy and bleeding results from safety population

Excess Number of Events
Pooled RECORD 1 – 4



Total VTE

Major VTE

Symptomatic VTE & All-Cause Mortality

Major Bleeding

Major bleeding + Surgical Site Bleeding

Any bleeding

Major or Non-Major Clin Rel Bleeding

Death from all causes

Any treatment-emergent serious AE

Excess # of events is based on Mantel-Haenszel-weighted treatment difference and is not identical to crude rate difference.

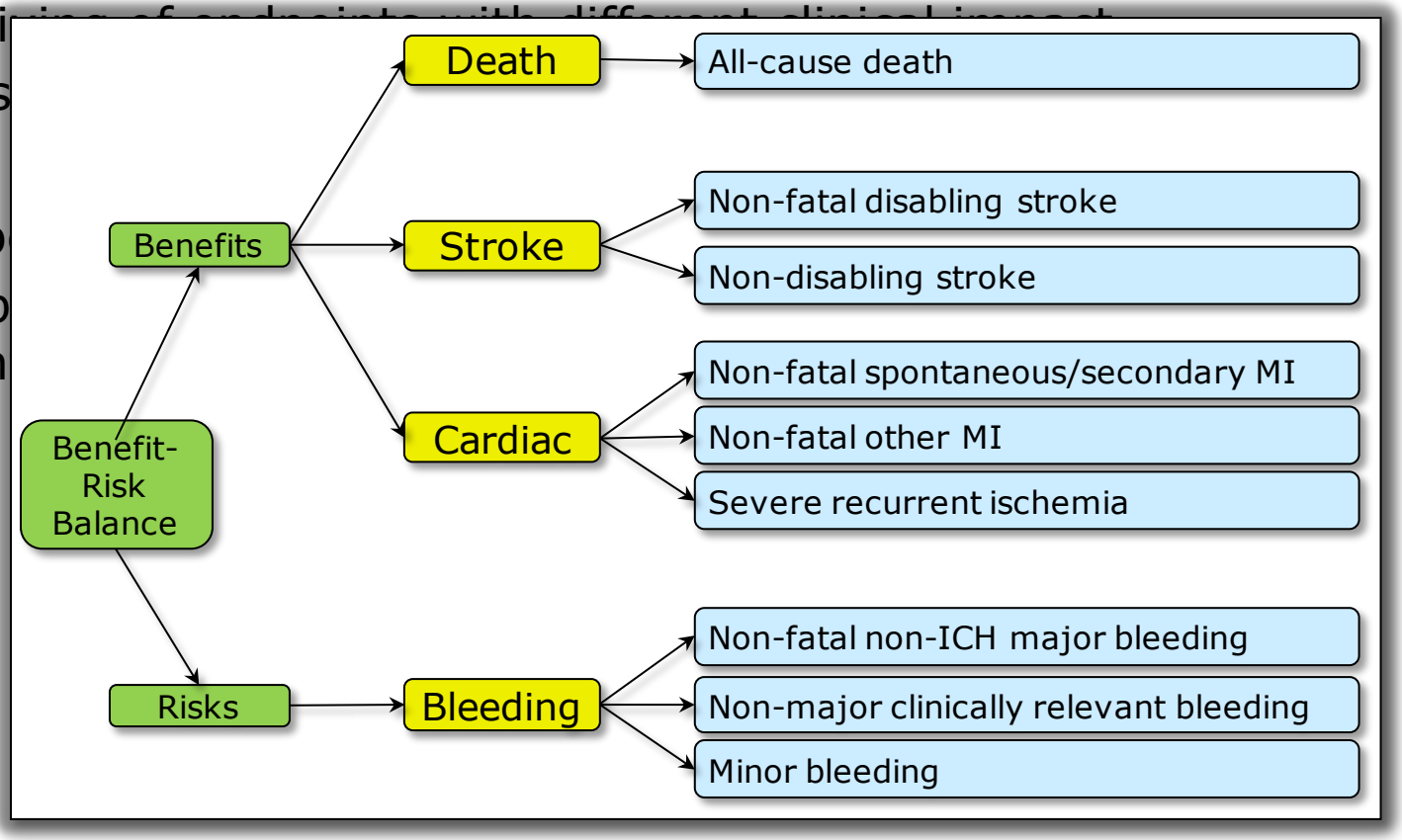
Total VTE and major VTE were based on the MITT populations and were prespecified endpoints; Symptomatic VTE, all cause deaths, treatment emergent bleedings and SAEs were based on the safety population; Total Duration Pool was used during treatment phase.

Full Value/Attribute Tree – Complete B-R Profile

- **Complete decomposition of all key benefits and harms**
- **Pros:**
  - Full transparency
  - No mixing of endpoints with different clinical impact
  - Aligns well with several structured approaches to B-R
- **Cons:**
  - Can be difficult to consider all endpoints at once
  - May be difficult to use for B-R decisions without assigning weights to each outcome

Full Value/Attribute Tree – Complete B-R Profile

- **Complete decomposition of all key benefits and harms**
- **Pros:**
  - Full transparency
  - No mi
  - Aligns
- **Cons:**
  - Can b
  - May b
    weigh



Rivaroxaban (XARELTO®)

Cardiovascular and Renal Drugs
Advisory Committee
September 8, 2011

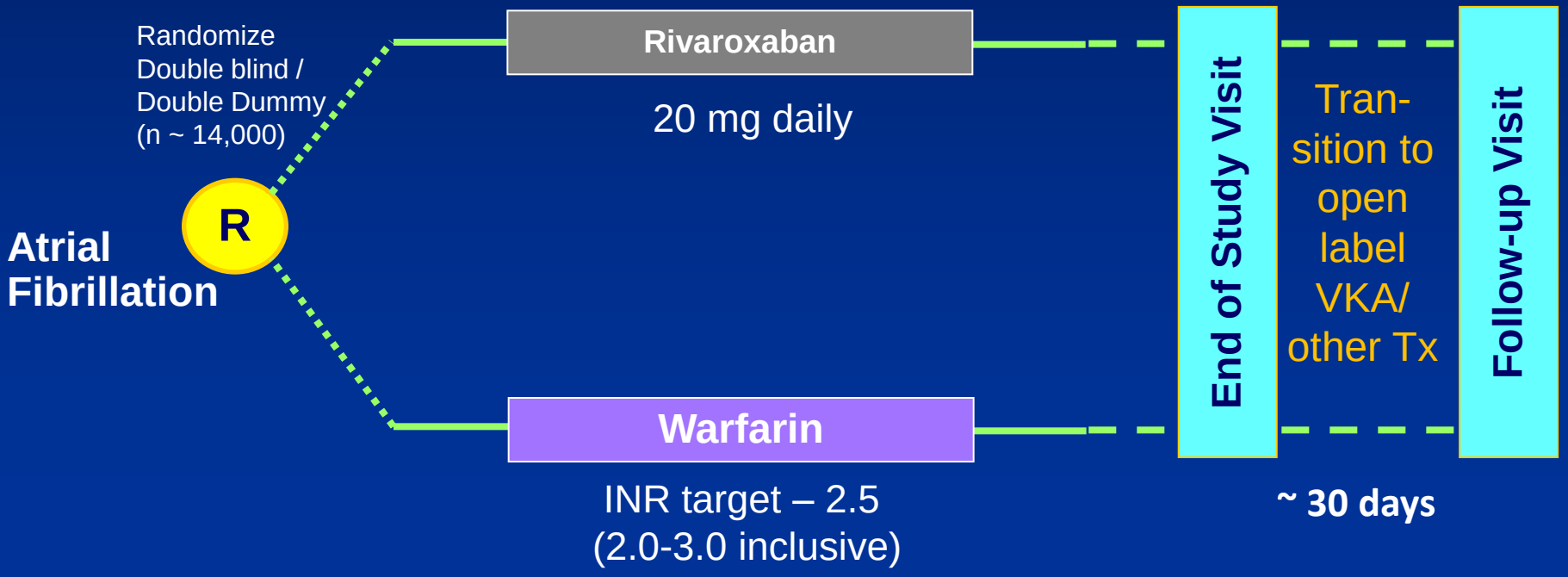
Johnson & Johnson
Pharmaceutical Research and Development, L.L.C.

ROCKET Study of rivaroxaban for Atrial Fibrillation Simplified Study Design

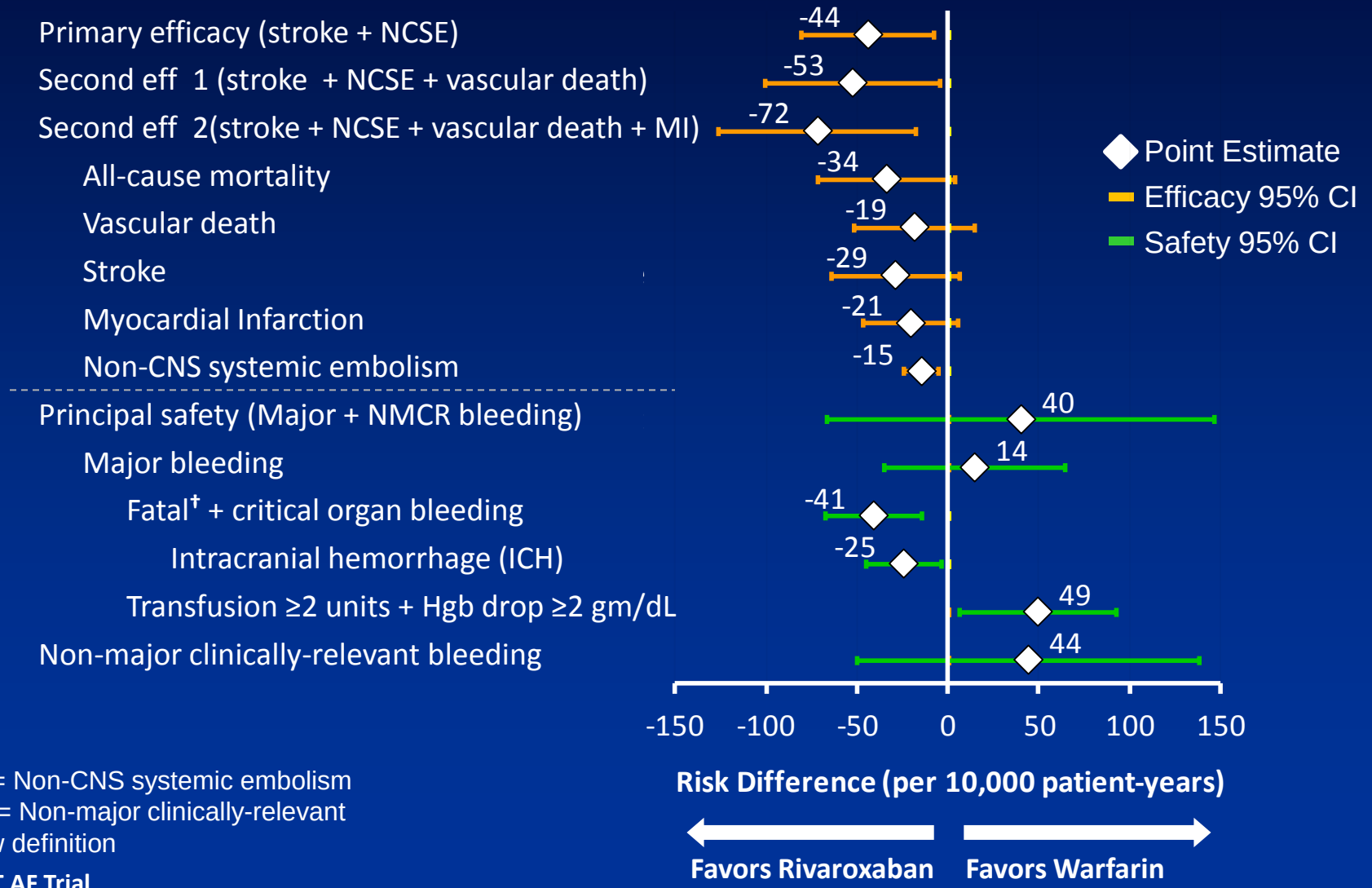
Risk Factors:
- CHF
- Hypertension
- Age >= 75
- Diabetes

At least 2 required

OR
- Stroke, TIA or systemic embolism



Risk Differences for Composite Endpoints and Components: Safety/On-Treatment



NCSE = Non-CNS systemic embolism
NMCR = Non-major clinically-relevant
†Narrow definition

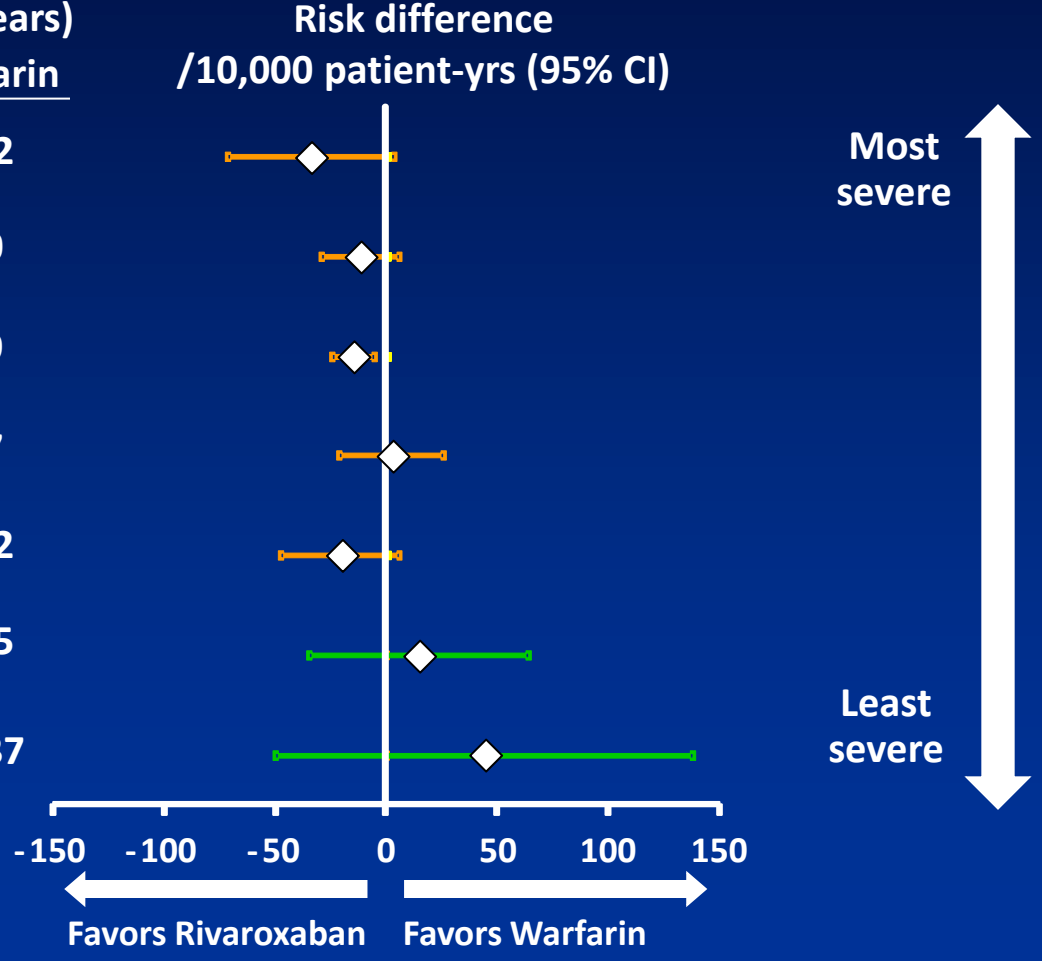
ROCKET AF Trial

What do Patients and Doctors Want?

- Long history of studies of preferences related to anticoagulation in general
- Generally patients and doctors rate outcomes in the following order
  - Death
  - Disabling stroke
  - Non-disabling stroke
  - Myocardial infarction
  - Major bleed
  - Minor bleed

ROCKET AF: Risk Differences by Clinical Severity/Impact†
Safety/On-Treatment

Endpoint	# of Events (/10,000 patient-years) Rivaroxaban	Warfarin
All-cause mortality	188	222
Disabling stroke	38	50
Non-CNS systemic embolism	4	19
Non-disabling stroke	79	77
Myocardial infarction	91	112
Major bleeding	360	345
Non-major clinically-relevant bleeding	1180	1137



† Endpoints in order of health state utility, a value that reflects preference for health states relative to perfect health and death. Values from Tufts' CEA registry.

Summary: Pragmatic Considerations for Endpoint Selection and Display in CV B-R

- **Typical efficacy and safety endpoints together are not always appropriate for benefit-risk assessment**
  - Efficacy Endpoints + Safety Endpoints ≠ Benefit-risk Endpoints

- **Different approaches to B-R endpoint selection in CV studies provide tradeoffs in ease of interpretation, transparency, ability to support decisions and ability to communicate**
  - Composite Net Clinical Outcome Endpoints
  - Pairwise Comparisons
  - Full Value/Attribute Tree