Shanghai Biostatistics Forum
Shanghai – December 4, 2017

上海生物统计学术论坛
上海 – 2017年12月4日

How the ICH E9 addendum may impact our clinical trials

ICH E9增补文件将给临床试验带来什么影响

Frank Bretz, Jiawei Wei, Liansheng Zhu (Novartis)
ICH E9(R1) Expert Working Group

Introduction
简介

- Draft E9 addendum has just been released
  E9增补草案刚刚发布
  - Significant impact on our work which requires a change of mindset
    将对我们的工作产生重大影响，需要我们改变思维模式
  - It proposes a framework for treatment effects to be more precisely specified, facilitating discussion between sponsor and regulator
    它提出了一个更精确地规定治疗效果的框架，以促进申办方和监管机构的讨论
- "Estimand" not a statistical topic, but a "drug development" topic
  “估计目标”不是一个统计问题，而是一个“药物研发”问题
- Failure to adequately address estimand questions can have severe consequences in our trials
  未能充分阐明估计目标问题将会给临床试验带来严重的后果

Treatment effect
治疗效果

[Section A.3.1]

How does the outcome of treatment compares to what would have happened to the same patients under different treatment conditions (e.g. had they not received the treatment or had they received a different treatment).

相同的受试者在试验治疗方案下的治疗效果与其它治疗方案（例如，与没有接受治疗或接受其它治疗的相比）相比结果如何?

Treatment effect
治疗效果

Suppose there are two treatments, A (active) and B (placebo).
假设有两种治疗方法：A（试验药）和B（安慰剂）

Hypothetical scenario: We know the outcome for each patient under both treatment conditions, A or B
假设情景：我们知道每一个患者在治疗方法A或B下的结果

- Patient 1 is perfectly adherent to whichever treatment s/he is assigned. The outcome is 9 on treatment A or 8 on treatment B.
  患者1完全依从他/她被分配的治疗。采用治疗方法A的结果是9， 治疗方法B的结果是8。

  What is the treatment effect?
  治疗效果是多少？

Treatment effect
治疗效果

Suppose there are two treatments, A (active) and B (placebo).
假设有两种治疗方法：A（试验药）和B（安慰剂）

Hypothetical scenario: We know the outcome for each patient under both treatment conditions, A or B
假设情景：我们知道每一个患者在治疗方法A或B下的结果

- Patient 2 adheres to treatment B with an outcome of 7, but discontinues if assigned to A (e.g. due to adverse events).
  患者2会依从于治疗方法B且治疗结果是7，但采用治疗方法A会提前终止（比如由于不良反应）

  What is the treatment effect?
  治疗效果是多少？

Treatment effect
治疗效果

Suppose there are two treatments, A (active) and B (placebo).
假设有两种治疗方法：A（试验药）和B（安慰剂）

Hypothetical scenario: We know the outcome for each patient under both treatment conditions, A or B
假设情景：我们知道每一个患者在治疗方法A或B下的结果

- Patient 3 adheres to treatment A with an outcome of 7, but discontinues if assigned to B (e.g. due to lack of efficacy) and takes rescue medication, with an outcome of 6 in the end.
  患者3会依从于治疗方法A且治疗结果是7，但采用治疗方法B会提前终止（比如由于缺乏疗效）并会服用应急用药且最终治疗结果是6

  What is the treatment effect?
  治疗效果是多少？

Treatment effect
治疗效果

Patients differ in response to treatment due to the occurrence of events after randomization ("intercurrent events")
因为随机化后发生的事件（“伴发事件”），不同患者对治疗的反应会有不同

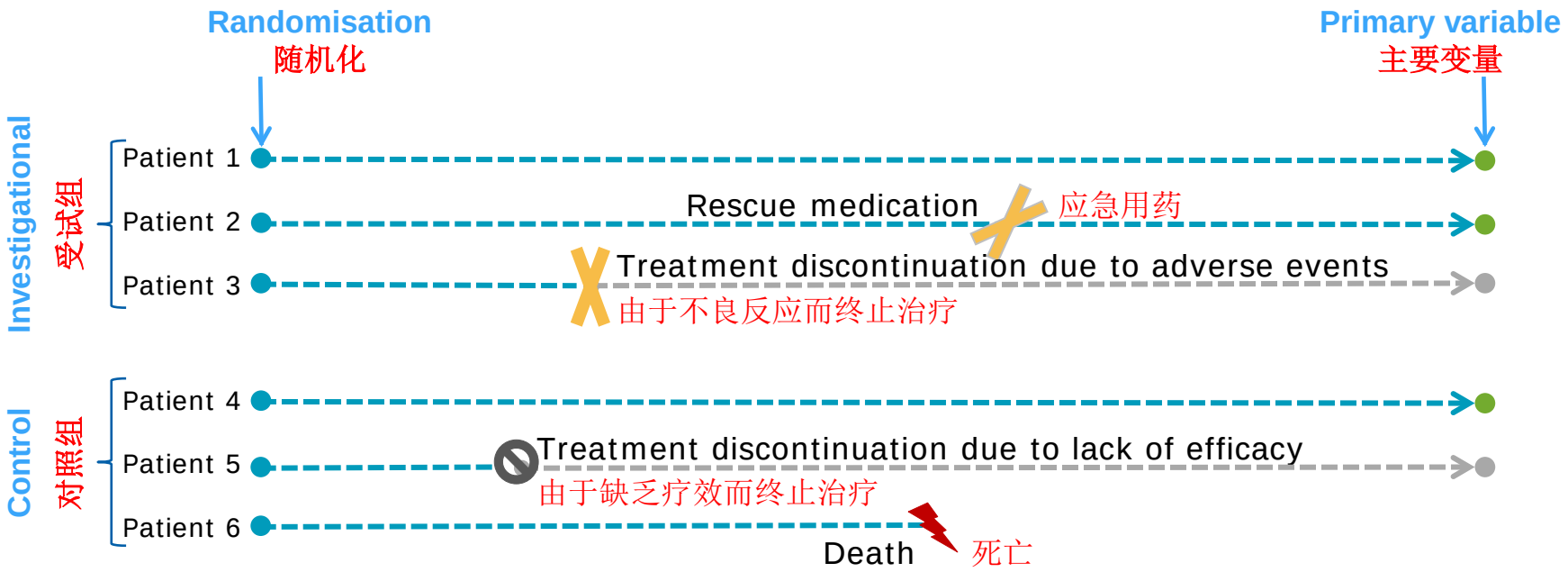
- Some patients will tolerate a medicine and adhere to its administration schedule, others will not

  对一种药物，有些患者可以耐受，并能遵守用药时间表，而有些则不能

- Some patients will require additional medication, others will not
  一些患者需要改变药物的剂量，或使用合并用药，而有些则不需要

- …

Treatment effect
治疗效果



How to define the treatment effect in the population of interest for the primary variable in the presence of intercurrent events?

当伴发事件存在时，如何定义目标人群在主要变量上所反映的治疗效果？

Intercurrent events
伴发事件

[Section A.3.1]

- Intercurrent events can present in multiple forms and can affect the interpretation of the outcome. For example,
  伴发事件可以以多种形式出现，并可影响目标变量的解释。例如，
  - if a patient dies before a planned measurement of blood pressure, the blood pressure will not be observed
    如果受试者在计划的血压测量时间点之前死亡，则不会观察到该时间点上的血压
  - if a patient takes rescue medication in addition to treatment, the blood pressure may be observed, but will reflect the combined effect of the treatment and the rescue medication
    如果受试者除了治疗之外还要服用应急用药，此时虽然能观察到血压，但这反映了治疗药物和应急用药的综合效应
  - if a patient discontinues treatment because of adverse events, the blood pressure may be observed but will reflect the lack of effect of the treatment when it is not taken
    如果受试者由于不良反应而终止治疗，则也能观察到血压，但这反映了在未用药时的情况

Intercurrent events
伴发事件

- Intercurrent events need to be considered in the description of a treatment effect on a variable of interest because both the value of the variable and the occurrence of the event may depend on treatment.
  在对感兴趣的变量所反映的治疗效果进行描述时，需要考虑伴发事件，因为变量取值和伴发事件发生可能都与治疗有关。
- The definition of a treatment effect should consider whether values of the variable after an intercurrent event are relevant, as well as how to account for the (possibly treatment-related) occurrence or non-occurrence of the event itself.
  在定义疗效时， 应当考虑伴发事件之后的所感兴趣变量的取值是否与之相关，以及如何处理伴发事件本身（可能是治疗相关的）的发生或不发生所带来的影响。

Dapagliflozin – for illustration
达格列净 – 例证

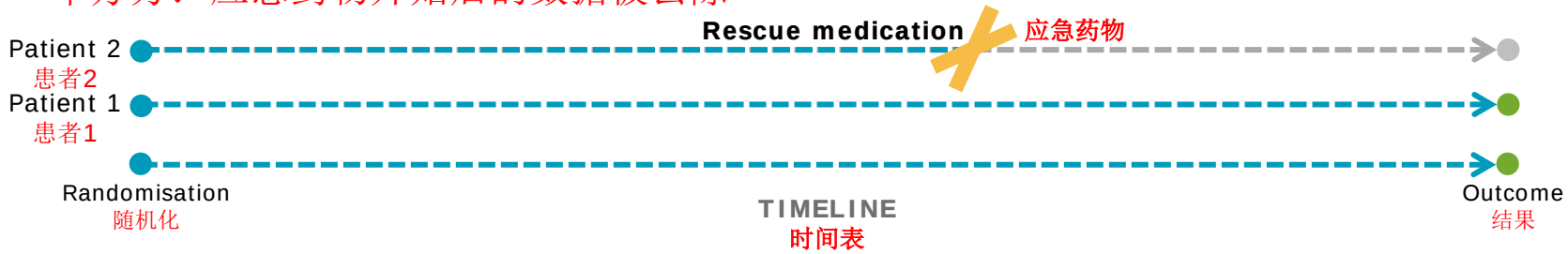
- Primary variable: Change in HbA1c from baseline to 24 weeks.
  主要变量：HbA1c从基线到24周的变化。
- Sponsor proposal: Data after initiation of rescue medication was excluded from the analysis.
  申办方提议：应急药物开始后的数据被排除在分析之外。
- *"While FDA has endorsed LOCF in the past, there is now more awareness of the limitations of this approach.* Instead I [used] the HbA1c outcomes regardless of rescue treatment, and no statistical adjustment is made for rescue. *This approach is also imperfect, but it comes closer to being a true ITT analysis ..."*
  "虽然FDA过去接受LOCF，现在对这种方法的局限性有了更多的认识。所以，不管是否使用了应急用药，我们并没有对此作出统计调整，而直接使用了HbA1c结果。这个方法虽然并不完美，但它更接近于意向性分析。"

LOCF = Last Observation Carry Forward：末次观察推进法

Dapagliflozin – for illustration
达格列净 – 例证

Different perspectives on the inclusion of data
关于数据包含的不同观点

– Sponsor: Remove data after initiation of rescue medication
申办方：应急药物开始后的数据被去除



– FDA: Include all data regardless of initiation of rescue medication
FDA：无论是否使用应急药物，都包含所有数据

Dapagliflozin – for illustration
达格列净 – 例证

Implied 'scientific questions of i[illegible]rest':
隐含的'感兴趣的科学问题'

- Sponsor: Attempt to estab[illegible]nt effect of the initially randomized treatments[illegible]ed rescue medication;
  在没有患者进行应急治疗[illegible]化的治疗的效果
- FDA: Compare treatmen[illegible]zin plus rescue' versus 'control plus rescue'.
  比较治疗方案'达格列净+应急治疗[illegible]+应急治疗'

Disagreement over what to estimate; <u>the estimand</u>.
对于要估计的对象意见不一致：估计目标。

ICH E9(R1)
ICH E9（增补）

- More than one ‘treatment effect’ can be described and estimated, raising questions like:

  多个‘治疗效果’可以被描述和估计，引发以下问题：

  - What is of interest for regulatory decision making?

    监管者决策的兴趣何在？

  - What do we need to communicate to prescribers?

    我们需要跟医生沟通那些问题？

  - Can we estimate those?

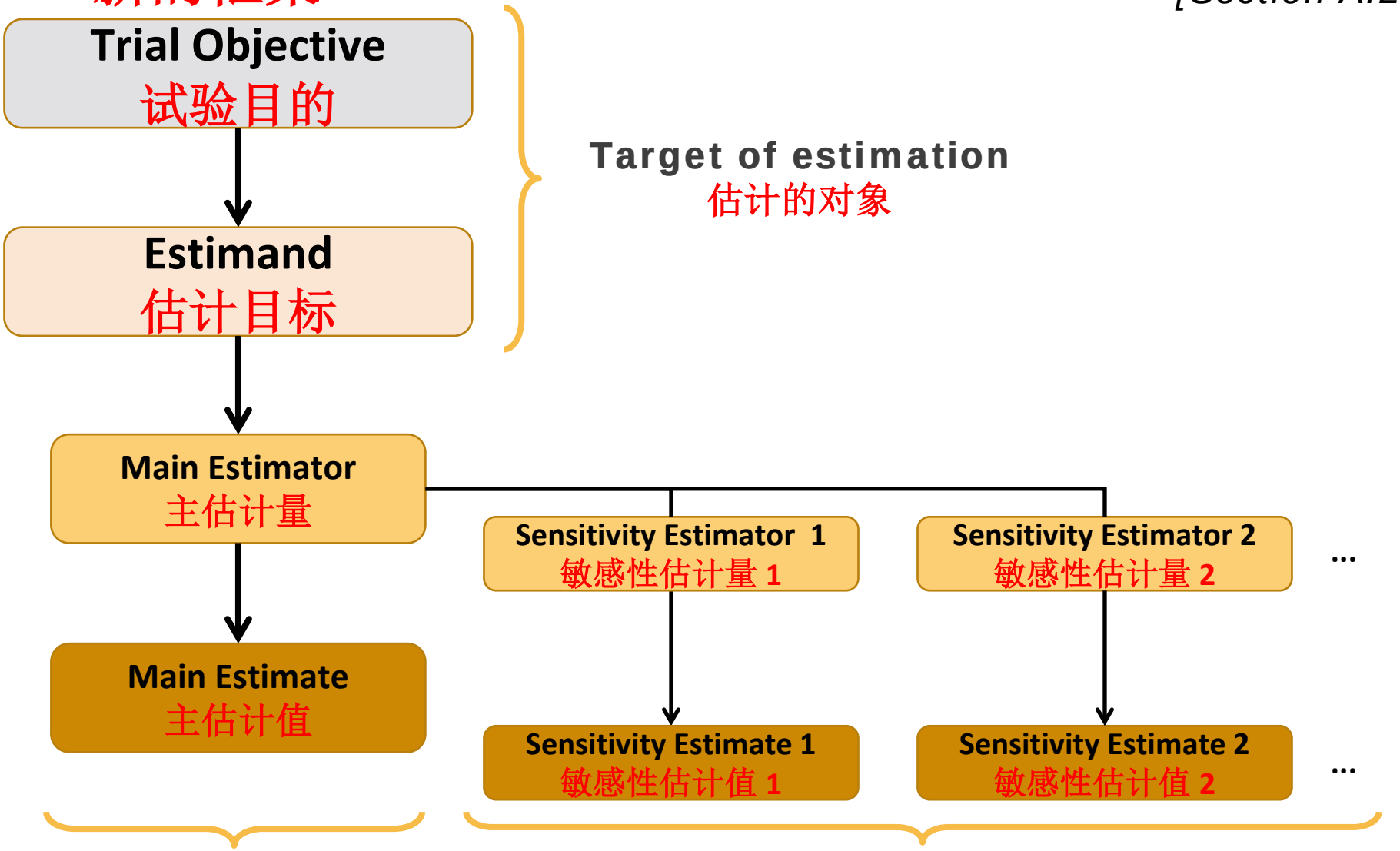
    我们可以估计这些治疗效果吗？

- This addendum helps aligning trial objectives with analysis methods in a coherent way, allowing for informed discussions with regulators

  这个增补文件有助于连贯一致地将试验目标与分析方法联系起来，从而允许与监管机构进行有实质内容的讨论

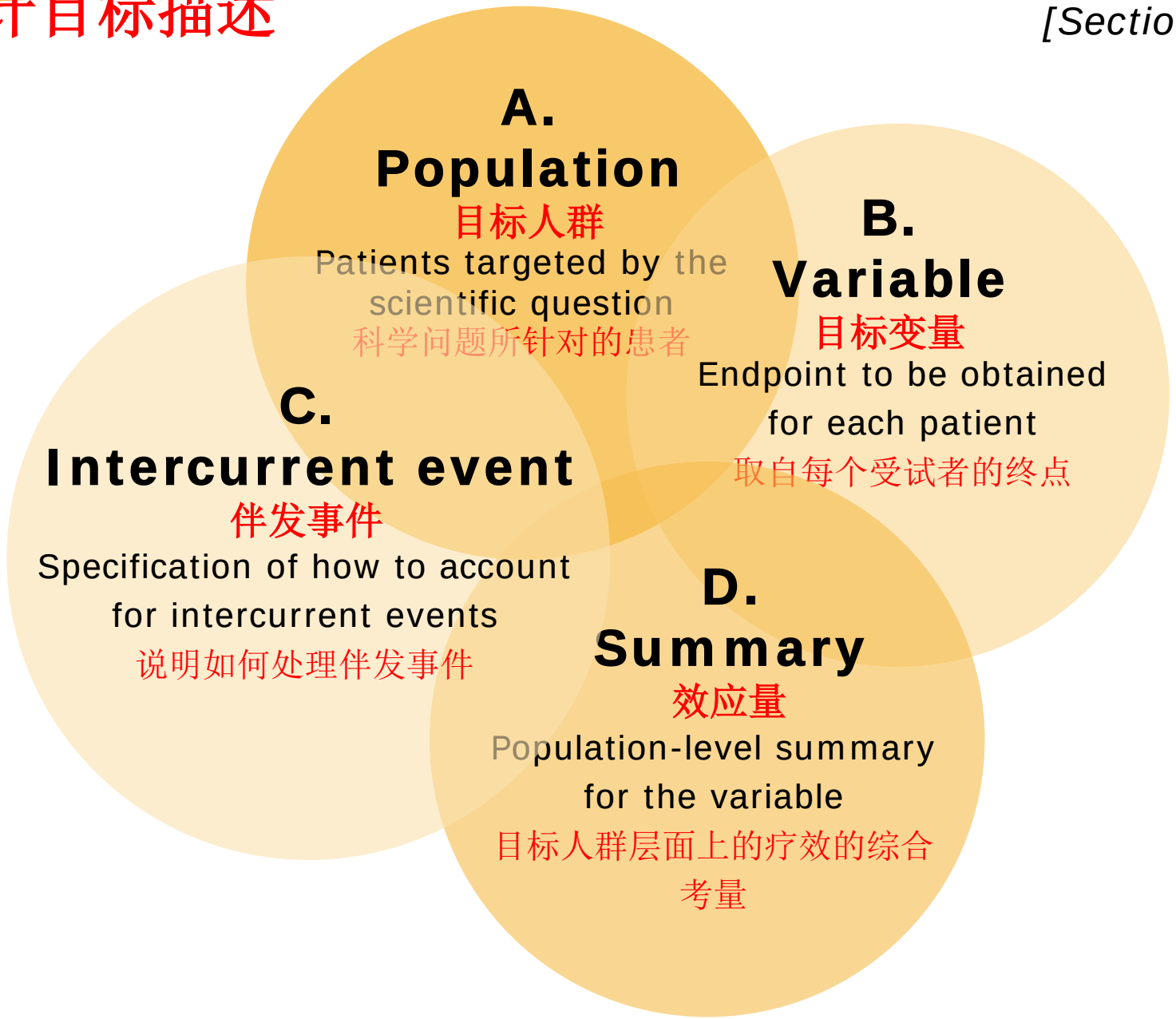
A new framework
新的框架

[Section A.2]



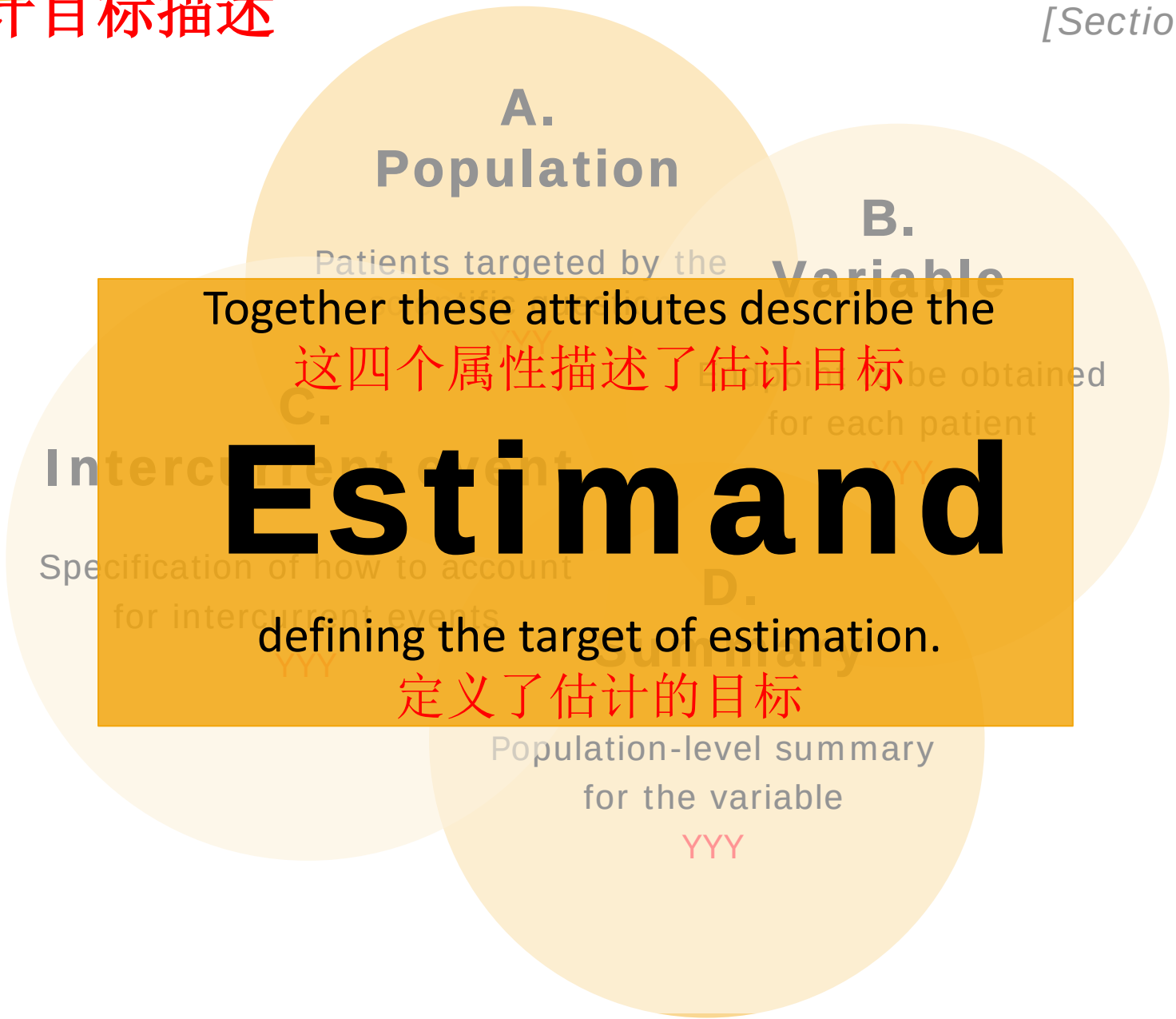
Estimand description
估计目标描述

[Section A.3.1]



Estimand description
估计目标描述

[Section A.3.1]



Together these attributes describe the

这四个属性描述了估计目标

Estimand

defining the target of estimation.

定义了估计的目标

Estimand strategies
估计目标策略

[Section A.3.2]

Altogether, five different strategies are considered. It is important to be precise when describing the preferred strategy for handling each intercurrent event.
增补文件一共考虑了五种不同的策略。描述处理每个伴发事件的首选策略时要精确到位。

1. **Treatment policy strategy:** The occurrence of the intercurrent event is irrelevant: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.
   疗法策略：伴发事件的发生是无关紧要的：无论是否发生伴发事件，均使用目标变量的值。
2. **Composite strategy:** The occurrence of the intercurrent event is taken to be a component of the variable, i.e. the intercurrent event is integrated with one or more other measures of clinical outcome as the variable of interest.
   组合策略：伴发事件的发生被认为是目标变量的一个组成部分，即伴发事件与临床结果的一个或多个其他测量结果整合为目标变量。

Estimand strategies
估计目标策略

[Section A.3.2]

3. **Hypothetical strategy:** A scenario is envisaged in which the intercurrent event would not occur: the value to reflect that scientific question of interest is that which the variable would have taken in the hypothetical scenario defined.
   假想策略：设想一种不会发生伴发事件的场景：反映科学问题的测量值定义为在假设场景中变量的定义。
4. **Principal stratum strategy:** The target population might be taken to be the principal stratum in which an intercurrent event would not occur. For example, the target population of interest might be taken to be the stratum of patients in which failure to adhere to treatment would not occur. In other words, a principal stratum is a subset of the broader population who would not experience the intercurrent event. The scientific question of interest relates to the treatment effect only within that stratum.
   主层策略：目标人群可认为是不会发生伴发事件的主层。例如，将不会发生不依从的受试者层定义为目标人群。换句话说，主层是不会经历伴发事件的更广泛人群的一个子集。科学问题仅限于在该层面的治疗效果。

Estimand strategies
估计目标策略

[Section A.3.2]

5. **While on treatment strategy:** Response to treatment prior to the occurrence of the intercurrent event is of interest. If a variable is measured repeatedly, its values up to the time of the intercurrent event may be considered to account for the intercurrent event, rather than the value at the same fixed timepoint for all subjects.
   在治策略：感兴趣的是在伴发事件发生之前治疗的反应。如果是重复测量变量，变量取值是伴发事件发生前的所有测量值，而不是所有受试者在相同的固定时间点的值。

Real examples
真实案例

- Example 1: Palliation in terminally ill cancer patients
  案例 1： 癌症晚期患者的缓和治疗

  (based on work/slides by Rob Hemmings, MHRA)
  （基于Rob Hemmings的工作/幻灯片，英国药品和健康产品管理局）
- Example 2: Treatment of chronic pain
  案例 2： 慢性疼痛的治疗

  (based on work/slides by Francesca Callegari, Novartis)
  （基于Francesca Callegari的工作/幻灯片，诺华）

Example 1 – Background (simplified)
案例 1 – 背景（简化版）

- Consider a new Drug X for palliation in terminally ill cancer patients. Symptomatic treatment a priori not expected to beneficially or detrimentally effect mortality.
  考虑用于癌症晚期患者的缓和治疗的新药X。对症治疗对死亡率的影响没有预期的先验信息
- Response on body weight and functioning after 12 weeks
  12周后对体重和功能的效应
- Scientific question of interest concerns the comparison in a randomized trial of Drug X to placebo.
  感兴趣的科学问题是药物X与安慰剂在随机试验中的比较
- Some patients will die during the 12-week follow-up. This is the intercurrent event.
  有些患者会在12周的随访中死亡。这是一个伴随事件
- Anti-cancer therapy used as background therapy in both treatment groups.
  两种治疗方法均以抗癌治疗为背景治疗

Example 1 – No intercurrent events
案例 1 – 无伴发事件

A. **Population**: defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval
目标人群：定义恰当的纳入/排除标准，确定目标受试人群

B. **Variable**: change from baseline after 12 weeks
目标变量：基线至12周的测量变化值

C. **Intercurrent events**: not expected to occur
伴发事件：不期望发生

D. **Summary measure**: difference in variable means
效应量：组间目标变量均数之差

Unrealistic not to expect any deaths
不期望任何死亡是不现实的

Example 1 – Treatment policy
案例 1 – 疗法策略

A. **Population**: defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval
目标人群：定义恰当的纳入/排除标准，确定目标受试人群

B. **Variable**: change from baseline after 12 weeks
目标变量：基线至12周的测量变化值

C. **Intercurrent events**: Regardless of death
伴发事件：不管是否死亡

D. **Summary measure**: difference in variable means
效应量：组间目标变量均数之差

How to measure response on body weight and functioning after death?
如何测量死亡后在体重和功能上的效应？

Example 1 – Composite
案例 1 – 组合策略

A. **Population**: defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval
目标人群：定义恰当的纳入/排除标准，确定目标受试人群

B. **Variable**: binary; alive and with maintenance of weight/functioning after 12 weeks
目标变量：存活12周后维持体重/功能作为二分类疗效指标

C. **Intercurrent events**: captured through the variable definition
伴发事件：变量定义中已考虑

D. **Summary measure**: difference in response proportions
效应量：不同处理组间有效率之差

Viable, but is it really a treatment failure if a patient lived reasonably well throughout 11 weeks and then dies?
可行，但如果患者在11周内生活得相当好，然后死去，那真的是治疗失败吗？

Example 1 – Hypothetical
案例 1 – 假想策略

A. **Population**: defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval
目标人群：定义恰当的纳入/排除标准，确定目标受试人群

B. **Variable**: change from baseline after 12 weeks
目标变量：基线至12周的测量变化值

C. **Intercurrent events**: had the patient not died
伴发事件：假设患者不发生死亡

D. **Summary measure**: difference in variable means
效应量：组间目标变量均数之差

How would a hypothetical scenario look like: Would the patient have continued treatment? Or discontinued treatment?
假设的情况是怎样的：患者会继续治疗吗？或停止治疗？

Example 1 – Principal stratum
案例 1 – 主层策略

A. **Population**: defined through subjects alive after 12 weeks, within the targeted population defined by inclusion/exclusion criteria
目标人群：在满足纳入/排除标准的目标人群中，12周之前均不发生死亡人群

B. **Variable**: change from baseline after 12 weeks
目标变量：基线至12周的测量变化值

C. **Intercurrent events**: captured through the population definition
伴发事件：在人群定义中考虑

D. **Summary measure**: difference in variable means
效应量：组间目标变量均数之差

Viable, but aren't we intrested in assessing the treatment effect even in those patients who died prior to week 12?
可行，但是我们对12周前去世的患者的治疗效果不感兴趣吗？

Example 1 – While on treatment
案例 1 – 在治策略

A. **Population**: defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval
目标人群：定义恰当的纳入/排除标准，确定目标受试人群

B. **Variable**: area under the curve for weight/functioning while being on randomised treatment
目标变量：随机化处理期间的体重/功能曲线下面积

C. **Intercurrent events**: captured through the variable definition
伴发事件：变量定义中已考虑

D. **Summary measure**: difference in variable means
效应量：组间目标变量均数之差

Reasonable estimand?
这是合理的估计目标吗？

Example 1 – Background (extended)
案例 1 – 背景（延伸版）

In reality, three relevant types of intercurrent events may occur:
在现实中，三种类型的伴发事件可能发生：

- death,
  死亡，
- change in background anti-cancer medicine,
  背景抗癌治疗的变化，
- use of additional symptomatic medication.
  使用附加的对症治疗药物。

The construction of an estimand should address each intercurrent event that may occur in the clinical trial and that will affect the interpretation of the results of the trial.
估计目标的构建应该阐明临床试验中可能发生的每个伴发事件以及相应处理方案，这将影响试验结果的理解。

Example 2 – Background
案例 2 – 背景

- Consider a new Drug X for patients suffering from chronic pain.
  考虑用于慢性疼痛患者的新药X
- Measured on an 11–point Numerical Rating Scale (NRS) for patient self-reporting of pain
  基于一个由患者自我报告的数值评定量表（11-point，NRS）的测量
- Scientific question of interest concerns the comparison in a randomized trial of Drug X to placebo
  感兴趣的科学问题是药物X与安慰剂在随机试验中的比较

Example 2 – Background
案例 2 – 背景

- Some patients will face intercurrent events not leading to study treatment discontinuation, but with potential confounding effects
  一些患者会面临不会导致终止治疗，但有潜在混杂效应的伴发事件
  - E.g. changes in doses of allowed concomitant medications for pain
    例如：允许使用的伴随用药剂量的改变
- Other patients will face intercurrent events leading to study treatment discontinuation
  另一些患者会面临导致终止治疗的伴发事件
  - E.g. adverse events (AEs), lack of efficacy (LoE), use of other concomitant medications or due to other reasons
    例如：不良反应，缺乏疗效，因别的原因使用其它伴随用药

Example 2 – Scientific question of interest
案例 2 – 感兴趣的科学问题

- Scientific question of interest guiding the primary estimand:
  感兴趣的科学问题指导主估计目标

  Estimate the treatment effect of Drug X against placebo for the target population on the primary variable. The treatment effect of interest shall
  估计药物X与安慰剂对目标人群在主要治疗变量上的治疗效果。治疗效果需要

  - be unconfounded by events which are deemed non-informative, e.g. changes in doses of allowed concomitant medications for pain
    不与无信息的事件混杂，例如：允许使用的伴随用药剂量的改变
  - account for the unfavorable outcome when patients are unable to continue taking the study drug due to an AE, LoE or use of other concomitant medications
    考虑到由于不良反应，缺乏疗效，使用伴随用药等等而不能继续服用研究药物的不良后果

Example 2 – Primary estimand
案例 2 – 主估计目标

***Key attributes** 关键属性*

A. **Population**: Patients suffering from the chronic pain condition at a moderate to severe disease stage. Patients may or may not be already on a concomitant medication for pain.
目标人群：中重度慢性疼痛患者。患者可能已经服用（或未服用）伴随药物治疗疼痛。

B. **Variable**: Change from baseline to last week of the study in weekly mean of the 24h average pain score measured by NRS
目标变量：基线至最后一周的平均24小时疼痛评分均值（基于NRS测量）的变化值

C. **Intercurrent events**: Events happening post-randomization, which can be an expression of how well the treatment works, but also of its safety and tolerability
伴发事件：随机化后发生的事件，可以反映治疗效果，但也反映了它的安全性和耐受性

D. **Summary measure**: Difference of variable means between Drug X and placebo
效应量：药物X与安慰剂之间目标变量均值之差

Example 2 – Primary estimand
案例 2 – 主估计目标

Details on attribute C 属性C的详细信息

We are interested in the treatment effect if patients:
我们对满足如下条件的患者的治疗效果感兴趣:

- would not change dose of allowed concomitant pain medications
  不会改变允许使用的伴随用药剂量
- are allowed to take short-acting pain relief medication
  允许服用短效止痛药
- would continue to be treated for the entire study duration unless forced to discontinue treatment due to
  将在整个研究期间持续接受治疗，除非因以下事件被迫停止治疗
  - adverse events
    不良反应
  - lack of efficacy
    缺乏疗效
  - use of other concomitant medications leading to treatment discontinuation
    使用其他导致终止治疗的伴随用药

Example 2 – Primary estimand
案例 2 – 主估计目标

***Justification** 理由*

Desire to quantify the treatment effect of the study drug where:
希望量化研究药物在以下情况的治疗效果：

- any potential confounders are removed, since these could lead to an attenuation or a dilution of the treatment effect of interest
  任何潜在的混杂因素都被消除，因为这些可能会削弱或淡化治疗效果
- the drug is taken for the stipulated duration, however
  按照规定的期限服用药物，然而
- we cannot ignore situations when a patient can no longer tolerate or benefit from the treatment (e.g. occurrence of AE, LoE, etc.), from whom a continuation of treatment would not be conceivable
  我们不能忽视患者不能忍受或不能从治疗中获益的情况（例如不良反应，缺乏疗效等等），对这些患者来说继续治疗是不可能的
- other patients who discontinued the drug due to other reasons could have theoretically continued to be treated without being put at undue risk
  其他由于别的原因而停止用药的患者，虽然在理论上可以继续治疗而不会被置于不适当的风险中

Example 2 – Further considerations
案例 2 – 进一步的思考

Statistical analysis
统计分析

- Primary analysis approach is in line with the primary estimand, including handling of changes in doses of allowed concomitant medication for pain and handling of missing data due to study treatment discontinuation
  主要分析方法应与主估计目标一致，包括处理伴随用药的剂量变化以及因终止治疗导致的缺失数据
- Sensitivity analysis targets the same estimand and is specified to assess the robustness of conclusions from the primary analysis
  敏感性分析针对同一估计目标， 用来评估主要分析结论的稳健性
- Supplementary analysis for a broader understanding of the treatment effect
  补充分析是为了对治疗效果有更广泛的理解

Example 2 – Further considerations
案例 2 – 进一步的思考

Necessary design features
必要的试验设计特点

- Information on changes in dose of allowed concomitant medications for pain
  关于伴随用药的剂量变化的信息
- Retrieved dropouts: data collected after study treatment discontinuation, if available
  脱落寻回：停止用药后收集的数据

A new framework
新的框架

Streamlined thinking for enhanced interaction, a common language.
新的框架提供了一致的思维方式以加强互动（一种通用的语言）。

- Interaction between statisticians and clinicians.
  统计师与临床医生的互动。
  - Some decisions should not be taken at the level of the statistical analysis, but before ➔ estimand;
    有些决定不应在统计分析的层面上进行，而应在更早的层面 -> 估计目标；
  - Description of estimand and choice of strategy are based on the clinical setting, mainly a clinician's decision;
    估计目标的描述和策略的选择都是基于临床试验的设置，主要是临床医生的决策；
  - The statistician should highlight when an estimand is difficult or impossible to estimate.
    当估计目标很难估计甚至不可能估计时，统计师应明确指出。

A new framework
新的框架

Streamlined thinking for enhanced interaction, a common language.
新的框架提供了一致的思维方式以加强互动（一种通用的语言）。

- Interaction between sponsor and regulators.
  申办方与监管机构的互动。
  - Framework will assist sponsor to design clinical trials;
    新的框架有助于申办方设计临床试验；
  - And regulators for assessment.
    且有助于监管机构的评估

Questions…