Estimand in China

- Consensus and Reflection from CCTS-DIA Estimand Workshop

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CCTS-DIA Estimand Workshop

Estimand
Population, variable, intercurrent event, summary

CCTS-DIA ICH-E9-R1/Estimand
南京研讨会

2017 年 10 月 14 号

	议题	报告人
会议主持：陈峰		
9:00 ~ 9:20	开幕致辞	
9:20 ~ 10:00	E9-R1 内容概览	戴鲁燕，邱婧君
10:00 ~10:10	茶歇	
会议主持：戴鲁燕		
10:10 ~ 10:30	糖尿病	成岗
10:30 ~ 10:50	肿瘤	殷悦
10:50 ~ 11:10	其他	刘恋
11.10-11:25	拯救用药	李杰
11:25 ~ 11:40	缺失数据	王瑞雪
11:40 ~ 12:00	试验方案和统计分析计划	邱婧君
12:00 ~ 13:00	午餐	
会议主持：邱婧君		
13:00 ~ 14:20	关键问题及翻译的讨论	陈峰
14:20 ~ 14:50	DIA Estimand 工作小组	戴鲁燕
14:50 ~ 15:20	DIA STAT Community	郭翔
14:50 ~ 15:00	会议总结	夏结来

CCTS-DIA Estimand Workshop

- ✓ The first time to discuss the topic of Estimand across companies and exchange with statistics KOLs
- ✓ Different levels of understandings and familiarities among workshop attendees;
- ✓ Consensus on basic concept framework to be introduced and alignment on translation of key terms
- ✓ Awareness and promotion of the concept implementation starting from the focused group

CCTS-DIA Estimand Workshop

Prior to the Workshop

- Taskforce and workshop organization
- Literature review and case collection

During the Workshop

- Introduction, presentation and sharing
- Discussion, debate and consensus

After the Workshop

- Wechat article of workshop summary
- Draft guidance translation
- SBF-DIA joint session on Estimand
- DIA China Annual Conference (in Planning)

Significance of Introducing Estimand

✓ Estimand provides a basis for **discussing various treatment effects**

- treatment policy under the intention to treat (ITT) principle
- randomization remains to be undisputable a cornerstone of RCT
- exploit the advantages of randomization to the greatest extent possible
- design and analysis to produce estimates that are reliable for decision making

✓ Issues considered generally under **data handling and missing data**

- Intercurrent events may render the later measurements difficult or irrelevant to interpret
- non-adherence with, or withdrawal from the treatment vs. discontinuation from the trial;
- measurements that exist but have not been collected vs. do not or cannot exist;
- basis for planning which data need to be collected and which not
- missing data handling aligned with the chosen estimand

Significance of Introducing Estimand

- ✓ **Concept of analysis sets** is considered
  - elimination of planned measurements vs. exclusion of subjects
  - a meaningful outcome value might not exist when subject has died
  - the meaning and role of per-protocol analysis
  - impact of protocol violations and deviations
  - treatment effect of interest →
    population of subjects to be included and
    the observations from each subject to be included

- ✓ **Concept of robustness** is given expanded discussion
  - the sensitivity of inference to the particular assumptions of a particular analysis vs. the choice of analytic approach more broadly
  - clarify by agreed estimand and a statistical analysis aligned
  - sensitivity to deviations from assumptions and limitations in the data in respect of a particular analysis

CFDA Is Collecting Public Comments on ICH E9-R1

国家食品药品监督管理总局药品审评中心
CENTER FOR DRUG EVALUATION, CFDA

当前位置：新闻中心>>工作动态>>通知公告>>新闻正文

关于公开征求ICH指导原则《E9(R1)：临床试验中的估计目标与敏感性分析》及《S5(R3)：人用药物生殖毒性检测》意见的通知

发布日期：20171128

ICH指导原则《E9(R1)：临床试验中的估计目标与敏感性分析》及《S5(R3)：人用药物生殖毒性检测》现进入第3阶段征求意见。按照ICH相关章程要求，ICH的监管机构成员需收集本地区关于第2b阶段指导原则草案的意见并反馈给ICH。

上述2个指导原则草案见附件，现向社会公开征求意见（反馈意见用中英文均可）。为与ICH工作组统一，建议反馈意见时主要针对ICH英文原文，可具体标明原文行号，中文翻译稿可作为参考。因时间仓促，译文质量难免有不足之处，故同时征求译文翻译意见。

社会各界如有意见，请于2018年2月28日前通过电子邮箱反馈至我办。

联系人：李新旭（E9(R1)），黄芳华（S5(R3)）

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ICH工作办公室

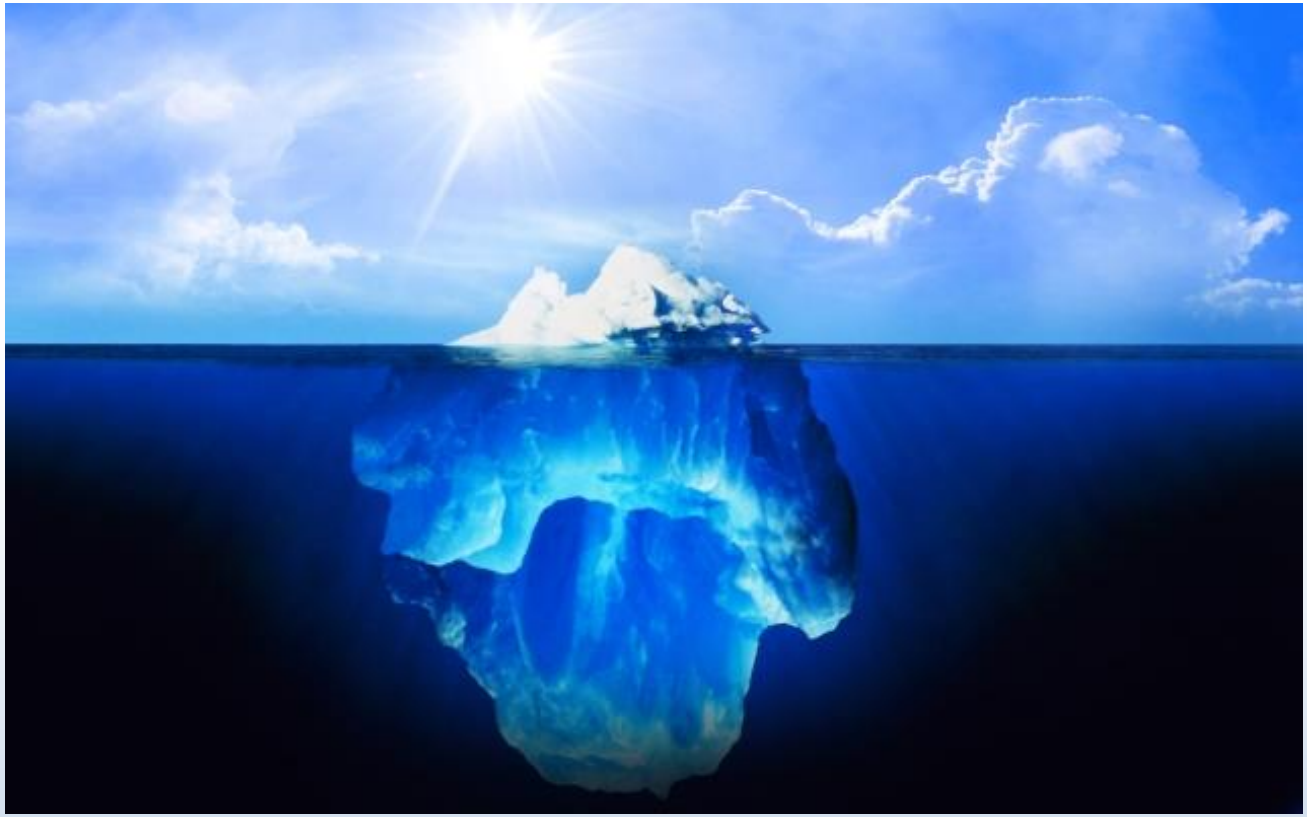
2017年11月28日

附件 1：	原文：E9(R1)：临床试验中的估计目标与敏感性分析.pdf
附件 2：	译文：E9(R1)：临床试验中的估计目标与敏感性分析.pdf

- ✓ CFDA is calling for public comments due by February 28th, 2018
- ✓ Both English and Chinese versions are available for review and comments

http://www.cde.org.cn/news.do?method=viewInfoCommon&id=314145&from=timeline&isappinstalled=0

Just a tip of the iceberg……



Estimand for All Type of Trials

- In E9-R1, there are two orthogonal aspects
  - A framework to **define estimands** and integrate them into trials,
  - **The choice of estimand(s)** that is/are appropriate for the trial.

- The interpretations of the framework and examples are primarily focused on confirmatory randomized clinical trials

- Limited elaboration on early phase exploratory trials
  - more flexibilities usually granted by the health authorities.
  - the analyses methods chosen and result interpretations for internal decision makings of the development program.

How do we foresee Estimand to be applied and implemented in as general applications to all type of studies, especially early phase?

Estimand for Early Phase Trials

- **Estimands in the early phase – is there a difference?**

- Not as simple as working backwards from the estimand(s) for the confirmatory phase

- Estimands in the early phase may differ
  - Population of interest
  - Endpoint
  - Measure of intervention effect

- But **implications for the late phase estimands** need to be considered
  - Unbiased measurement within early phase trial of late phase estimand
  - Prediction of late phase estimand (population, measure of intervention effect)
  ➔ **Late Phase success probabilities**

Estimands for Early Phase Trials

- **Population of interest**
  - Early phase population compared to late phase might be
    - Totally different (HV vs patients)
    - Similar but different (slightly different/sentinel)
    - Similar/equal (same target population)
      - Type of centres?

- **Determination of population of interest** for late phase could be an objective of early phase

  - Enrichment/Adaptive enrichment

Estimands for Early Phase Trials

- **Endpoint of interest**
  - Late phase might be rather “easy“
    - Agency/registration-driven
    - **Diffences for different regions?**

  - **Early phase more complicated**
    - Still would like to have clinically relevant endpoint
      - But no reason why confirmatory endpoint has to be used
      - Surrogacy of chosen endpoint
    - Should also be efficient
      - Scale of interest
      - Continuous vs dichotomized endpoint
    - Sometimes even not clinically relevant or validated
      - Biomarker
    - These aspects might contradict each other

Estimands for Early Phase Trials

➢ Example scale of interest regarding endpoint

- Continuous vs dichotomized endpoint (80% power, alpha=0.1)
  - SD=1.0, effect=0.4 => **114** pts needed total

Rate control	Rate experimental	N total
15.8%	27.4%	225
30.9%	46.0%	185
50%	65.4%	184
69.2%	81.6%	216
84.1%	91.9%	311
94.5%	97.9%	568

- In many cases continous endpoint is more efficient than dichotomized one

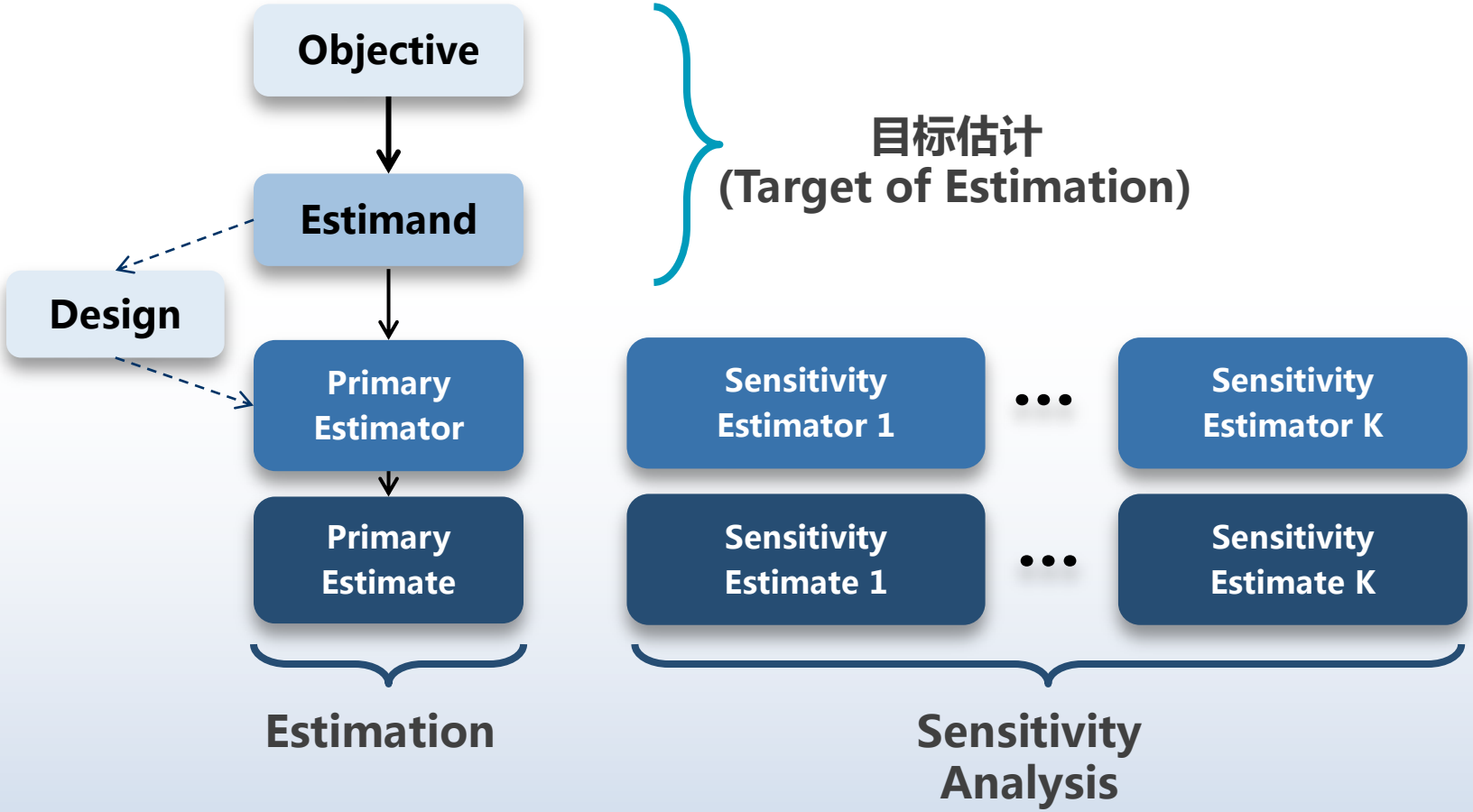
Estimands for Early Phase Trials

➢ Measure of intervention effect

- Early phase often **“efficacy“** (per-protocol) estimand more of interest
  - Clearer “go/no-go for PoC
  - How to estimate de-jure estimand?

- Scale of interest
  - Ratio vs difference vs odds ratio

Relevance to Other ICH Guidance



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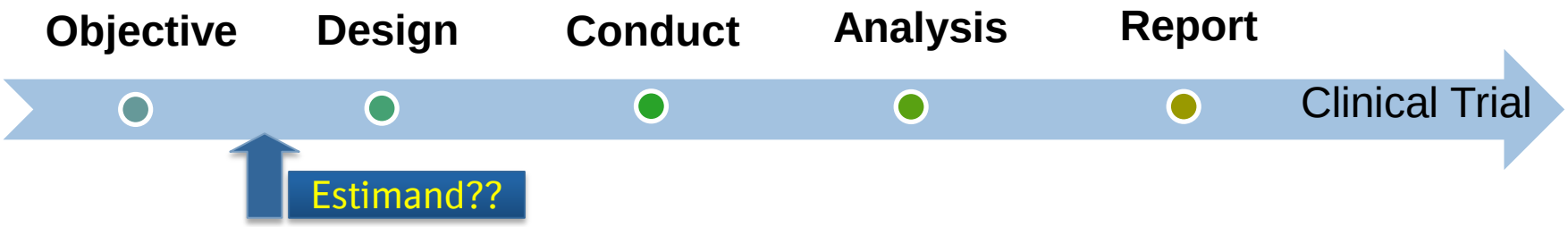


From ICH E8:

- ✓ **Objective:** may include exploratory or confirmatory characterisation of safety and/or efficacy and/or assessment of PK parameters and etc.
- ✓ **Design:** should include parallel group, cross-over, factorial, dose escalation and fixed does-dose response (ICH E4, E6, E9 and E10)
- ✓ **Analysis:** method of subject allocation, the measurement methods for response variables, hypotheses to be tested, analytical approaches and etc.
- ✓ **Reporting:** ICH E3 and E6

Relevance to Other ICH Guidance

- As outlined in E8, key design aspects include
  - selection of subjects
  - selection of control
  - number of subjects
  - response variables
  - methods to minimize or assess bias

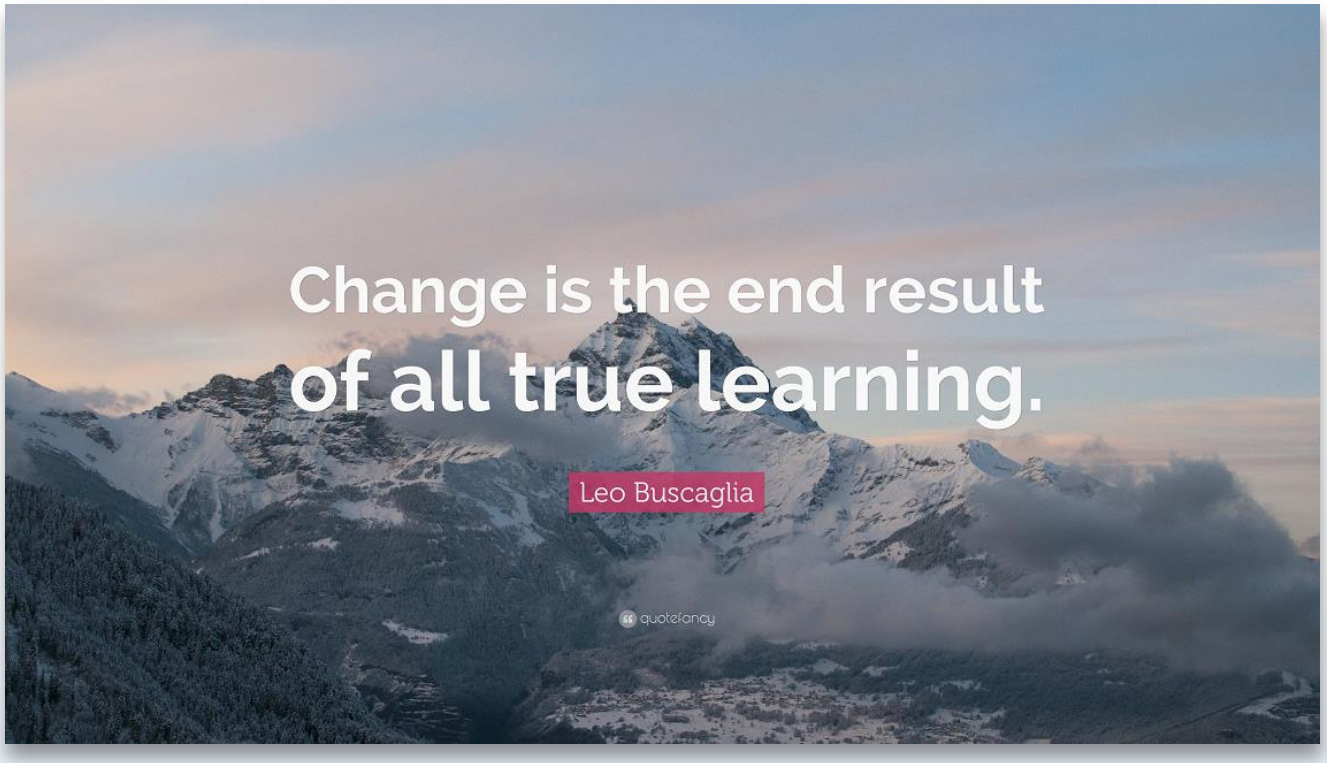
- The proposed framework of Estimand intends to bridge the connection between the objective and design.

- It is unclear in the current draft how the four elements of Estimand inform the design aspects given **that Estimand is not constructed based on these design aspects**

Relevance to Other ICH Guidance

- Choice of control is outside the formal scope of the 4 components of the estimand, although it should probably be part of the estimand definition somewhere?
- Several designs that are valid for addressing the same estimand; e.g. a parallel vs. a crossover trial
- The estimand is therefore can not be deterministic for the trial design, just a set of criteria that need to be met. Likewise for an analysis; there are sometimes several methods that address the same estimand but under different assumptions.

Will future update of E9 R-1 or E8 elaborate and explain further?



Read, Share, Exchange, Discuss!

Acknowledgement

- ✓ Prof. Chen Feng and CCTS working group
- ✓ DIA Estimand Working Group
- ✓ Colleagues at BI:
  - James Bell
  - Frank Fleisure