ICH E17　国際共同治験の計画及びデザインに関する一般原則

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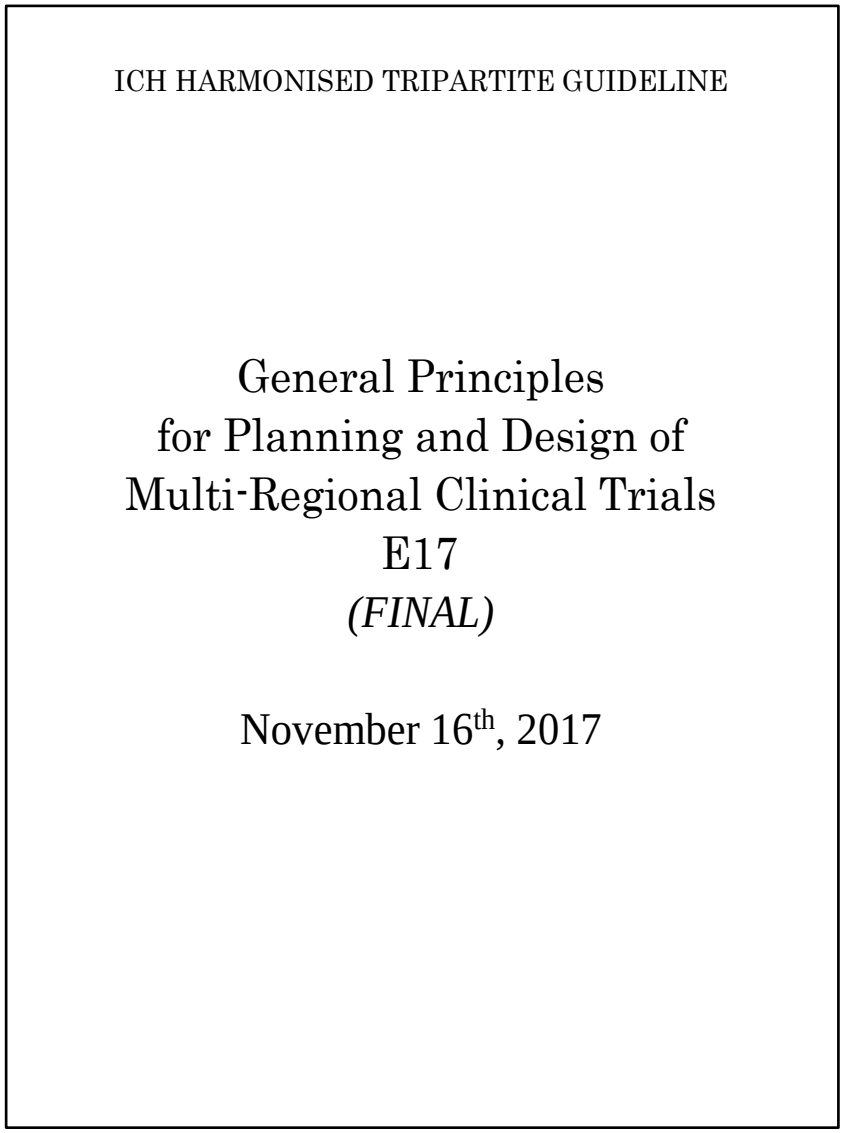
ICH E17 guideline


ICH HARMONISED TRIPARTITE GUIDELINE

General Principles
for Planning and Design of
Multi-Regional Clinical Trials
E17
(FINAL)

November 16th, 2017

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- 2016年6月　ガイドライン案公開
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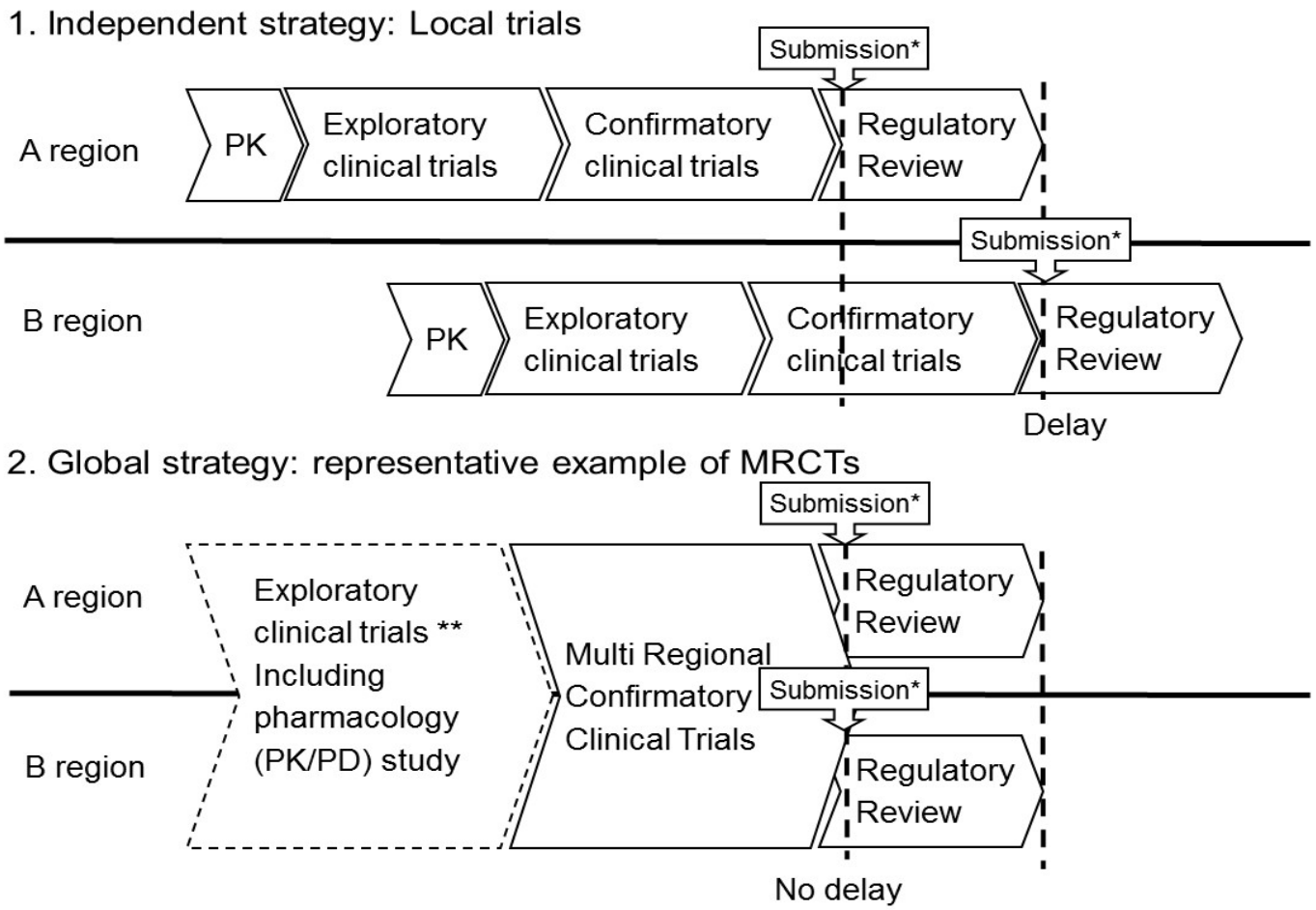


Figure 1. Illustrations of clinical drug development workflow across regions for drug submission and regulatory review in independent and global strategies

*: Marketing Authorization Application/New Drug Application

**: Could be parallel single region trials or MRCTs

1.4. Basic Principles

1.4. Basic Principles (1)

1. Strategic use of MRCTs in drug development programmes, properly designed and executed according to this guideline, can increase efficiency of drug development. MRCTs may enable simultaneous submission of marketing authorisation applications and support regulatory decision-making in multiple regions, allowing earlier access to new drugs worldwide. Although MRCTs may generally become the preferred option for investigating a new drug for which regulatory submission is planned in multiple regions, the potential for regional differences to impact the interpretability of study results should be carefully considered.
2. The intrinsic and extrinsic factors important to the drug development programme, should be identified early. The potential impact of these factors could be examined in the exploratory phases before the design of confirmatory MRCTs. Information about them should also be collected during the confirmatory trial for evaluation of their impact on treatment effects.

1.4. Basic Principles (2)

3. MRCTs are planned under the assumption that the treatment effect applies to the entire target population, particularly to the regions included in the trial. Strategic allocation of the sample size to regions allows an evaluation of the extent to which this assumption holds.
4. Pre-specified pooling of regions or subpopulations, based on established knowledge about similarities, may help provide flexibility in sample size allocation to regions, facilitate the assessment of consistency in treatment effects across regions, and support regulatory decision-making.
5. A single primary analysis approach for hypothesis testing and estimation of the overall treatment effect should be planned so that it will be acceptable to all concerned regulatory authorities. A structured exploration to examine the consistency of treatment effects across regions and subpopulations should be planned.

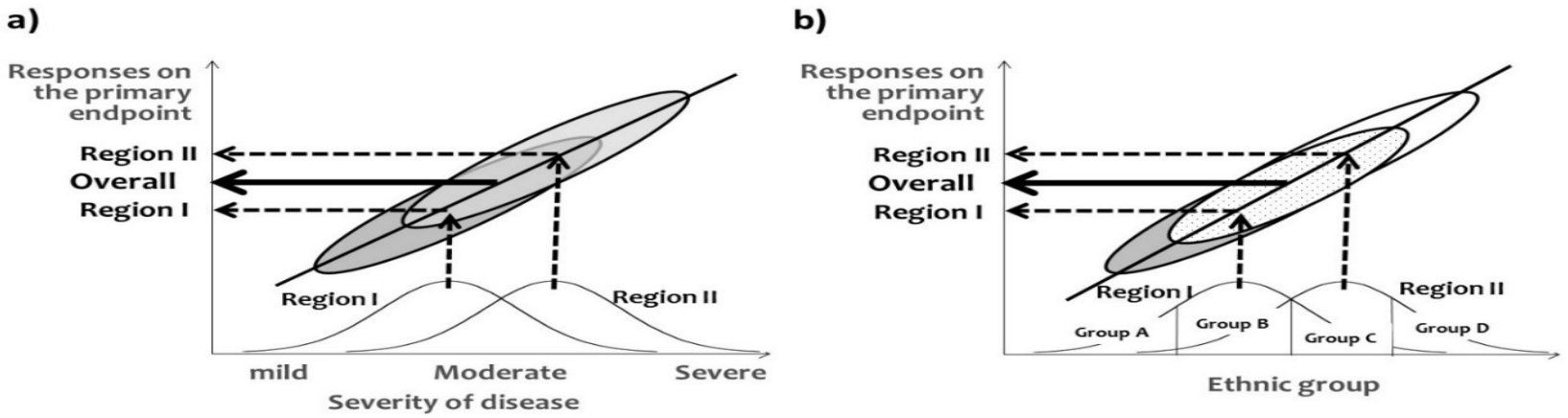
1.4. Basic Principles (3)

6. In light of diverse regional practices, ensuring high quality of study design and conduct in accordance with ICH E6 in all regions is of paramount importance to ensure the study results are interpretable. Careful attention to quality during trial planning, investigator training, and trial monitoring will help achieve consistently high trial quality required for a successful MRCT.
7. Efficient communication among sponsors and regulatory authorities is encouraged at the planning stage of MRCTs, with the goal of obtaining acceptance of a global approach to study design across the different regulatory regions.

Major points
Described in Section 2

2.2.1 Pre-consideration of Regional Variability and its Potential Impact on Efficacy and Safety

- At the planning stage, regional variability, the extent to which it can be explained by intrinsic and extrinsic factors, and its potential to influence the study results, should be carefully considered in determining the role MRCTs can play in the drug development strategy.
- Figure illustrates that regional differences in treatment response can be explained by differences in the distribution of the underlying factor (disease severity) between regions (a) or in the ethnic distribution of the regions(b) .



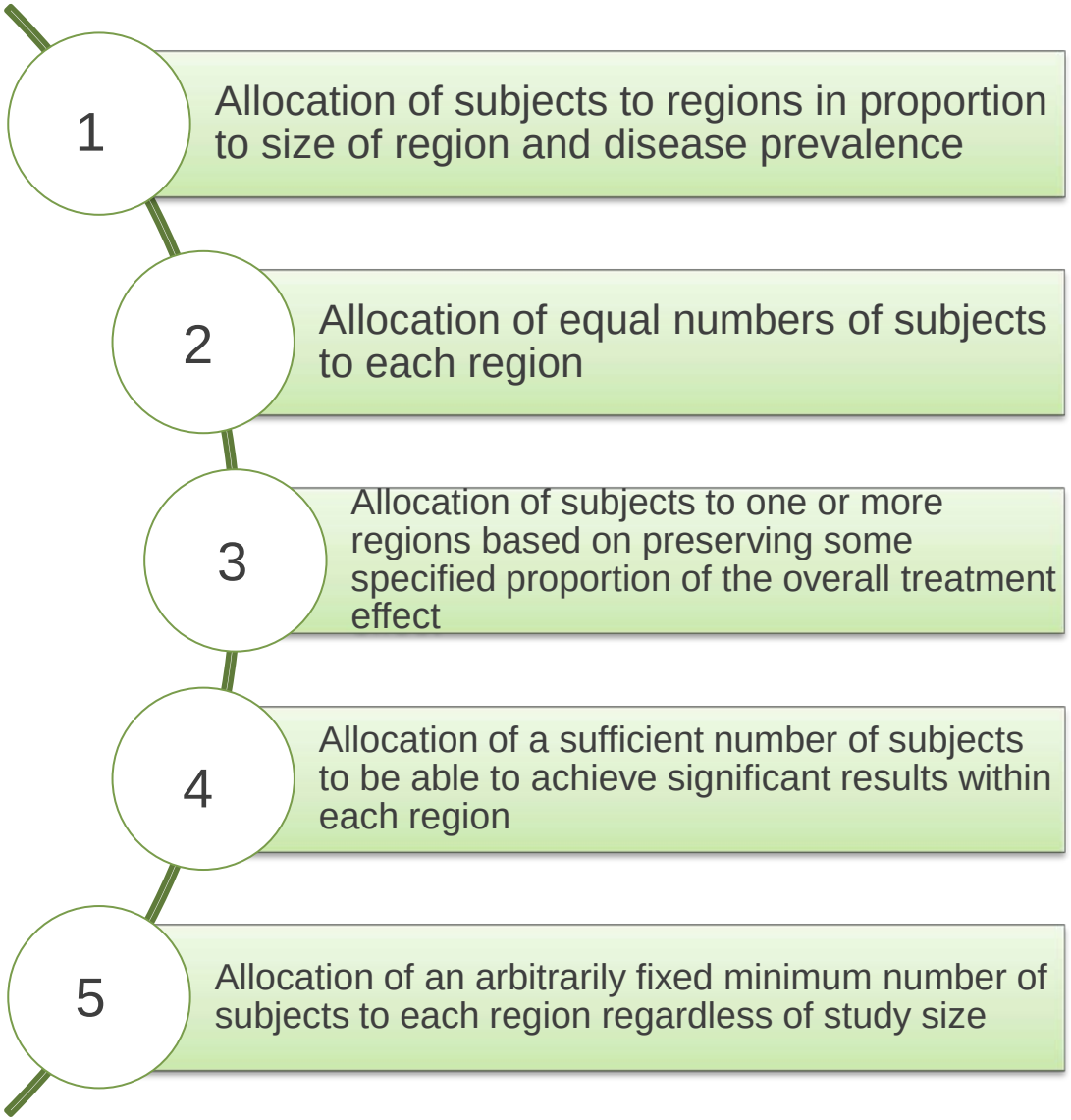
2.2.3 Selection of Doses for Use in Confirmatory MRCTs

- It is important to execute well-planned early development programmes that include PK and/or PK-PD studies of applicable parameters, in order to identify regional differences which may impact dose selection.
- The dose regimens in confirmatory MRCTs (based on data from studies mentioned above) should in principle be the same in all participating ethnic population.
- If earlier trial data show a clear difference in dose-response and/or exposure-response relationships for an ethnic population, it may be appropriate to use a different dosing regimen, provided that the regimen is expected to produce similar therapeutic effects with an acceptable safety margin, and provided it is scientifically justified in the study protocol. Prospective careful planning of assessment strategies where different doses are used should be tailored to each case and described in the analysis plans.

2.2.5 Sample Size Planning

- The key consideration for sample size planning, is ensuring sufficient sample size to be able to evaluate the overall treatment effect, under the assumption that the treatment effect applies to the entire target population, particularly to the regions included in the trial.
- MRCT offers a unique opportunity to evaluate the extent to which this assumption holds.
  - MRCTs are usually stratified by region for both randomization and analysis.
- Consistency of treatment effects across regions is evaluated, and if clinically relevant differences are observed, there should be further exploration to determine if these differences can be attributed to differences in intrinsic or extrinsic factors (see Section 2.2.7).
- These considerations should be reflected in the overall design of the MRCT and will influence the sample size planning and allocation to regions.

2.2.5 Five examples for sample size allocation to region



- A balance between #1 and #2 is recommended to ensure that recruitment is feasible and able to be completed in a timely fashion, but also to provide sufficient information to evaluate the drug in its regional context.

2.2.5 Pooled Regions and Subpopulations

- Pooled regions:

Pooling some geographical regions, countries or regulatory regions at the planning stage, if subjects in those regions are thought to be similar enough with respect to intrinsic and/or extrinsic factors relevant to the disease and/or drug under study.

- Pooled subpopulations:

Pooling a subset of the subjects from a particular region with similarly defined subsets from other regions whose members share one or more intrinsic or extrinsic factors important for the drug development programme at the planning stage. Pooled subpopulations is assumed as ethnicity-related subgroup particular important in the MRCT setting.

2.2.5 Pooled Regions and Subpopulations

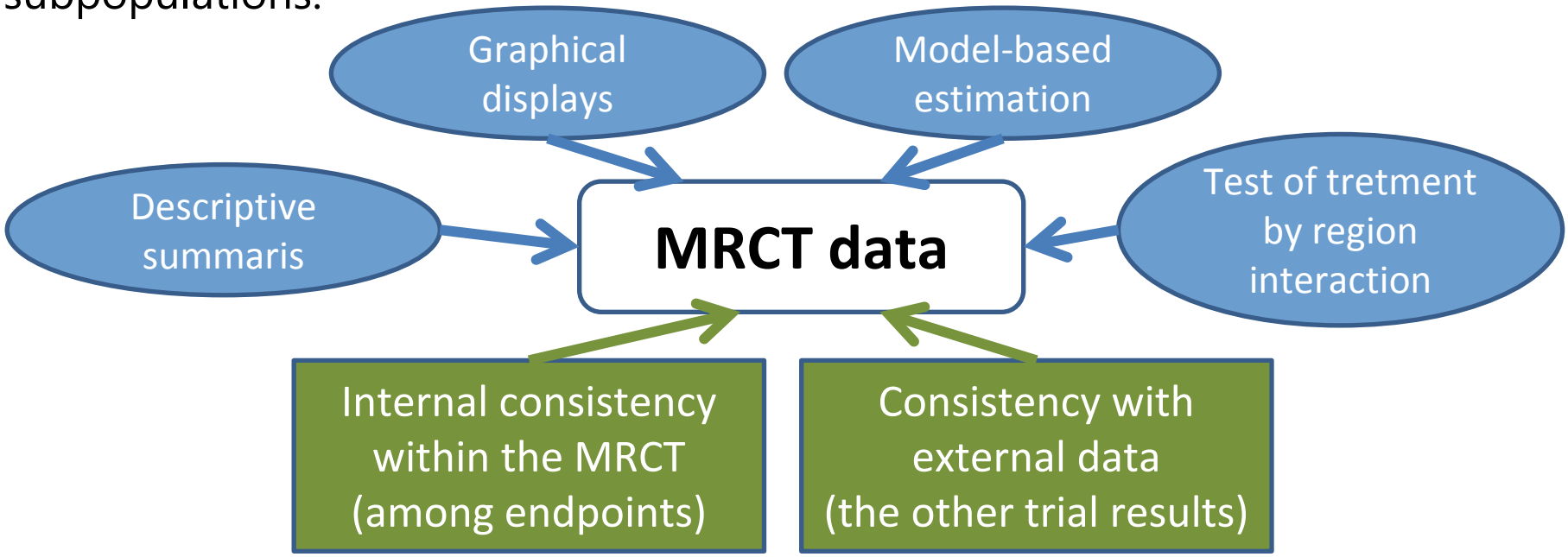
- Pre-specified pooling of regions or subpopulations may help provide flexibility in sample size allocation to regions, facilitate the assessment of consistency in treatment effects across regions, and support regulatory decision-making.
- The pooling strategy should be justified based on the distribution of the intrinsic and extrinsic factors known to affect the treatment response, and the disease under investigation and similarity of those factors across regions.
- For example, pooling Canada and the United States into a North American region is often justified because of similar medical practices and similar use of concomitant medications. Pooling strategies should be specified in the study protocol and statistical analysis plan, if applicable.

2.2.7. Statistical Analysis Planning

- The analysis strategy should be planned to enable the qualitative and/or quantitative evaluation of benefit/risk across regions or important subpopulations represented in the MRCT.
- In planning an MRCT, the primary analysis strategy should carefully consider (1) the target population, (2) the endpoints/variables of primary interest, (3) the relevant intrinsic and extrinsic factors in the multi-regional, multi-subpopulation context and (4) the population-level summary of data required to describe the treatment effect. For most MRCTs, the primary analysis will correspond to a test of the hypothesis about the treatment effect and the estimation of that effect, considering data from all regions and subpopulations included in the trial.

2.2.7 Consistency Evaluation

The statistical analysis strategy should include the evaluation of the consistency of treatment effects across regions and subpopulations. For this purpose, consistency in treatment effects is defined as a lack of clinically relevant differences between treatment effects in different regions or subpopulations.



The evaluation of regional consistency is not considered a confirmatory exercise but rather a gateway for further exploration

2.2.7. Statistical Analysis Planning

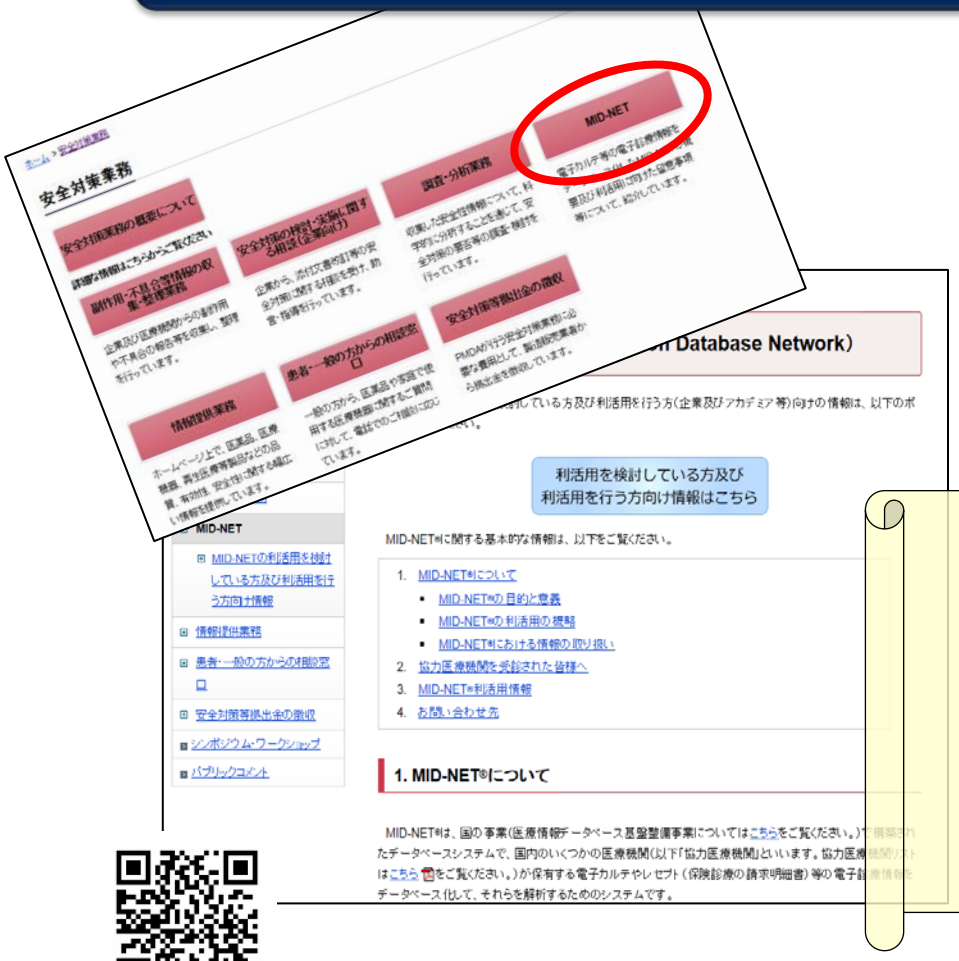
- In case of clinically relevant differences in treatment effects among regions, a structured exploration of these differences should be planned.
  - Factors known a priori to vary among regions and hypothesized to be prognostic or predictive should be planned for and evaluated in the analysis model.
    - e.g.; disease severity, race, other subject characteristics (e.g., smoking status, body mass index), medical practice/therapeutic approach (e.g., different doses of concomitant medications used in clinical practice) or genetic factors (e.g., polymorphisms in drug metabolising enzymes)
  - Even with careful planning, unexpected regional differences may be observed, and post-hoc analyses should be used for further investigation. Factors known to be prognostic for the disease would be examined first
  - Regional differences not explained by examination of known factors may require further post-hoc investigation to either identify plausible reasons for the differences or to better understand the observed heterogeneity. In some cases, additional data, including data from other clinical trials, or supportive evidence from other sources, may be needed to understand the regional differences observed.
  - These eventualities should be carefully considered at the planning stage.

Impacts of E17 guideline

- **Earlier access to innovative therapies**
  - Provide an innovative drug earlier to patients by synchronizing the timing of clinical drug development across different regions
- **Avoid duplication**
  - Reduce the need to conduct standalone regional or national studies including bridging studies.
- **Promote international harmonization**
  - A globally harmonized approach to drug development should be considered first.
- **Provide better evidences for drug approval in each region**
  - Encourage better planning and design of MRCTs based on the latest scientific knowledge and experiences
- **Longitudinal build-up of capability and infrastructure for global drug development**
  - Planning and conducting high quality MRCTs throughout drug development will build up trial infrastructure and capability

Information

https://www.pmda.go.jp/safety/mid-net/0001.html
※11月1日より公開中（MID-NET®に関する情報を順次追加しています）



- **PMDA web site**
  http://www.pmda.go.jp/index.html
- **E-mail:**
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MID-NET®運用開始記念シンポジウム
～医療リアルワールドデータ活用の幕開け～

日　時：平成30年2月26日（月）13:00～18:00（予定）
場　所：日本消防会館（ニッショーホール）
東京都港区虎ノ門２丁目９番１６号
※　詳細については後日PMDAホームページで公表

MID-NET® に関する紹介ページのQRコード

ご清聴ありがとうございました。