老年人群参与创新药临床试验的关键要素及试验设计要点（试行）

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October 2025

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I. Overview

The elderly are significant beneficiaries of drug treatment. Organ and life functions in the elderly...

Impaired physiological function, reduced drug processing ability, increased sensitivity to drugs, and decreased tolerance.

Decreased libido, coexistence of multiple diseases and polypharmacy, and self-risk management ability.

Their strength is also relatively weak, therefore, when drugs are used on the elderly, their safety and efficacy are questionable.

The features of efficiency and ease of use are particularly important.

According to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (International...

Council for Harmonisation of Technical Requirements for

Pharmaceuticals for Human Use (ICH) published the E7 Special Populations...

Research: The guidelines in Geriatrics require that, for widespread use in the elderly population...

Drug research needs to be conducted across all age groups, including the elderly.

The older the patient population, the more necessary it is to include elderly individuals in the study.

People in their 30s.

In most clinical trials of innovative drugs, there is a representative elderly population.

The inadequacy of the existing system fails to adequately address the medication needs and physiological characteristics of the elderly population.

The experimental design elements, such as the location and pathological state, were not included in the experimental data analysis.

The specific consideration of evaluations for the elderly population makes it difficult to apply trial data to the drug.

It provides good evidence for assessing the benefits and risks of using the product in older populations.

This guidance aims to address the needs of older adults under the premise of full implementation of ICH E7.

Key elements and trial design involved in group-participant clinical trials of innovative drugs

The key points in the plan do not cover the entire process of drug clinical trials or are related to drug clinical trials.

All content related to trial design. In this guideline, the "older population" refers to those ÿ65 years of age.

crowd.

This guidance only represents the current views and understanding of drug regulatory authorities and is not intended to be construed as such.

It has mandatory legal binding force. With the advancement of basic medical research and clinical trial technology...

As technology evolves, the relevant content in this guideline will be continuously improved and updated.

Encourage sponsors, researchers, and drug regulatory authorities to actively communicate and discuss.

II. Population Representativeness

(a) Common Applicable Scenarios

Drug clinical trials involving elderly populations typically involve the following scenarios: ÿ Treatment

Treatment or improvement of chronic or recurrent diseases that severely affect quality of life (such as high blood pressure, high cholesterol, high blood sugar ... cholesterol, high blood sugar)

Blood pressure, diabetes, osteoporosis, chronic obstructive pulmonary disease, chronic pain, sleep

ÿ Treatment or improvement of vital organ function (sleep disorders, anxiety, depression, etc.)

Degeneration or functional impairment (such as Alzheimer's disease, age-related macular degeneration, chronic...)

(e.g., impaired cardiac, liver, and kidney function); ÿ Treatment of diseases prevalent in the elderly.

Acute and critical illnesses (such as acute myocardial infarction, stroke, etc.) or malignant tumors; ÿ needles

Comprehensive treatment of comorbidities or associated functional abnormalities (such as type 2 diabetes mellitus)

And cardiovascular diseases); ÿ Use of drugs in routine medical procedures (such as anesthetics,

muscle relaxants, contrast agents, etc.

In the research and development of medications for the elderly, especially in response to the aforementioned situations...

When conducting drug development, it is encouraged to consider obtaining support within the overall clinical research plan.

Based on research data on medication use among the elderly.

(II) Age Group Division

Taking full account of clinical treatment needs, disease pathogenesis, and pathophysiology

Epidemiological characteristics, pharmacokinetic and pharmacodynamic characteristics are factors in drug selection.

The general principles for dividing the elderly population into different age groups in drug clinical trials. If we consider...

The above factors do not indicate a clear age-related difference; therefore, it is advisable to consider using actual age groups.

The age range can be divided into categories such as 65-74 years old, 75-84 years old, and 85 years old and above.

If existing evidence supports age-group targeting for drugs with the same mechanism/target, it can provide a basis for nano-targeting.

This provides supporting evidence for the age range of the elderly population.

Considering the need for individualized and precise treatment in clinical practice, the participation of the elderly in invasive procedures...

New drug clinical trials may involve classification based on an individual's actual aging status.

The method employs objective physiological and functional health measurement indicators or characterization tools.

To reflect the biological age of the elderly population.

For example, frailty is often used in geriatrics to describe the progression of age.

Decreased or disordered physiological reserve function, increased vulnerability of the body, and reduced stress resistance

A state of diminished vitality and weakened ability to maintain homeostasis. Compared to chronological age,

Frailty assessment tools are used to characterize the frailty status of the older population, and then based on the frailty status...

The method of stratifying trial participants can be considered as being based on actual age.

The supplement to the partitioning method not only helps to meet the currently commonly used method based on solid feet

The requirements for drug benefit-risk assessment in age-related diagnosis and treatment can also contribute to individualized clinical practice.

Precision medicine requires research data that can be referenced. Currently, there are already drug clinical trials...

Try using the Short Physical Performance Status Scale (SPS).

Battery degradation (SPPB), pacing test, degradation index, and Fried degradation phenotype, etc.

Assessment tools, as a further supplement to demographic factors of the older population, but

Tools and standards supporting frailty assessment are not yet widely used in clinical diagnosis and treatment and pharmaceuticals.

In clinical trials.

Regarding the selection of supplementary representation tools beyond actual age, or whether to accept them...

For self-developed characterization and evaluation tools, it is recommended to communicate with drug regulatory authorities. Ideal.

Characterization tools should have the power to determine physiological function and require sufficient samples.

The quantity is verified and is easy to understand and operate.

(iii) Inclusion and exclusion criteria for the test

In principle, participants in drug clinical trials should be able to fully represent and

Reflecting the characteristics of the actual user population after the drug is marketed, to ensure the drug is used by the target population.

The effectiveness and safety of the group were fully assessed. In cases involving older adults...

In clinical trials of new drugs, obtaining trial data directly from this age group is crucial.

Yes, it can also support comparative analysis between older adults and non-older adults.

Encourage the appropriate inclusion of older adults in the early stages of clinical research and development, in order to prepare for future clinical trials.

Continued research plans will be supported by data.

When formulating inclusion and exclusion criteria for innovative drug clinical trials involving older populations,

Sufficient clinical evidence or scientific basis is required to support this. If some of the selected [entrants]...

If the exclusion criteria are not necessary, they should be considered for deletion or modification to avoid unnecessary exclusion.

Limiting the inclusion of older adults ensures the representativeness of the study population. For example, when it is necessary to...

Elderly patients with severely impaired organ function should be excluded to avoid uncontrollable risks.

In such cases, exclusion criteria should be set based on specific organ dysfunction standards to avoid incorporating...

Elderly individuals with only mild functional impairments were excluded.

Generally, the older the expected patient population (especially those involving long-term use), the better.

(In cases involving long-term or lifelong medication), it is especially necessary to include elderly patients in clinical trials.

The target population is typically 75 years of age and older. If the trial protocol specifies an age range...

If limited, the reasons for not collecting experimental data from the very elderly population should be explained.

In the overall clinical research strategy, the confirmatory research phase is usually retained early.

Most of the inclusion and exclusion criteria were used in the two-phase study. However, due to the two-phase study...

The objectives and experimental designs may differ; inclusion and exclusion criteria are usually more specific in the early stages of research.

Therefore, the design of confirmatory studies should fully consider early [procedures/procedures].

The applicability of the standards at each stage should be considered to avoid directly applying them and hindering the participation of the elderly population.

To avoid unnecessary restrictions.

In real life, the elderly population is often at high risk of developing comorbid diseases and taking multiple medications.

In clinical trials of innovative drugs involving the elderly population, inclusion and exclusion criteria...

The design should comprehensively consider comorbidities and concomitant medications. The trial protocol should be based on...

Based on the characteristics of the disease and the general situation of the target age group for treatment, it is clearly stipulated that...

Whether and how to include these elderly people to ensure their representativeness.

In addition, non-clinical research data and early clinical research data of the drug (such as...)

Pharmacokinetics and safety, tolerability studies, drug interaction studies, etc.

and the known benefit-risk assessment results of drugs with the same mechanism/target in the elderly population.

All of these can serve as the basis for formulating inclusion and exclusion standards for the elderly population.

(iv) Experimental index design

In drug clinical trials involving older adults, although the observed indicators may...

Similar to that of adults, but some special factors still need to be considered. For example, for those who can...

Objective efficacy indicators for measurement may need to focus on the delayed effects of drug action.

and changes after discontinuation of medication; while for subjective efficacy indicators based on individual feelings or performance.

If the target is the same, then the difference in efficacy must be considered. If the same observation indicator is being observed...

The data results for the elderly population differ significantly from those for the general adult population, and this should be clarified.

The clinical significance of these differences (e.g., whether rapid onset of action is required, or whether a certain level of efficacy is required)

Based on a certain standard of improved subjective experience, the reasons for the differences should be fully analyzed.

And assess whether the drug dosage regimen needs to be adjusted to meet clinical treatment needs.

In addition to the same observation indicators as those for general adults, the elderly population...

Clinical trials may also require the design of specific efficacy or safety observation indicators.

The target, especially in trials that include older adults (e.g., 75 years and older).

These specific indicators typically include the impact on cognitive function and the exacerbation of comorbidities.

Conditions include decreased function of vital organs, improved quality of life, and mortality rate.

The inclusion of these indicators helps to more comprehensively assess the effects of drugs on older adults.

Effectiveness and safety, thereby better meeting the clinical needs of this special population.

III. Research Strategies

(a) Collecting relevant data in clinical pharmacology studies

In innovative drug development, it is often through organs that become more prominent with age.

Physiological changes in function are used to characterize the main differences between the elderly and general adults.

They are different. For example, the decline in gastrointestinal absorption function with age can...

It can lead to a decrease in the bioavailability of drugs absorbed through the stomach or intestines.

Clinical trials of innovative drugs involving older adults will involve collecting samples from older adults.

Pharmacokinetic data are used to analyze the pharmacokinetic effects of drugs in the elderly population.

While studying behavior, it supports comparative analysis of the relationship between drug exposure and effect (including establishing...).

(Use of simulation methods).

Liver or kidney dysfunction can occur in people of all ages, but in...

It is more common in the elderly population. The development of innovative drugs generally needs to include treatments for liver or...

A study on medication use in patients with renal insufficiency to support the determination of dosage regimens and

Identification of safety risks. If the drug has already been tested in patients with liver or kidney dysfunction...

Clinical trials of similar drugs, or studies demonstrating the effects of drugs targeting the same mechanism on liver or kidney function.

If there is relatively definitive evidence of its influence on the entire population, then, when considering liver and kidney function...

When elderly individuals in declining health participate in clinical trials, it is important to consider their known liver or kidney function.

Research data on individuals with functional impairments should be used to rationally design inclusion and exclusion criteria and refine risk control measures.

Develop a plan.

Routine drug interaction studies can provide insights for innovative drugs in the elderly.

The use within the population provides research evidence. Meanwhile, innovative drugs involving older adults...

In clinical trials, the results can also be used to determine the drugs that are permitted to be used together in the trial.

Research evidence is provided to determine whether there are clinically significant interactions between investigational drugs.

For example, maintaining a stable combined dosage from the start of the trial, and administering the investigational drug.

Previously, after the investigational drug reached steady-state exposure, blood levels of the combined drug were measured.

Trough concentrations were measured and compared before and after; significant changes indicated a potential problem with the medication.

The possibility of interaction.

(ii) Collect relevant data in exploratory and confirmatory experiments.

In drug clinical trials, the inclusion strategy for the elderly population should be based on the drug...

The study should be designed appropriately based on the characteristics of the material and the research objectives to ensure the reliability of the results.

And extrapolation. For drugs used to treat typical geriatric diseases or diseases common in the elderly population.

Sufficient quantities of [specific substances] should be included in exploratory and pivotal clinical trials, and [the following should be noted:] [Specific substances] should be included in [specific quantities] ...

Representative elderly patients. The same method is generally used for both the elderly and non-elderly populations.

For drugs, possible research design approaches include: comparing elderly individuals with non-elderly individuals.

Including older adults in the same study for joint analysis, and in the trial...

The elderly population was included in the trial as a parallel/embedded cohort independent of the non-elderly population.

And conduct independent evaluations and carry out independent research on the elderly population, etc.

1. Non-independent elderly population trials

Non-independent elderly population trials refer to trials that simultaneously include elderly individuals.

The group and the general adult population. These types of trials primarily involve two design schemes.

The first approach uses a stratified randomization design, based on age or certain important organs.

Functional status is stratified based on key factors. This design approach facilitates comparative analysis.

The effect differed between older adults and general adults, but due to the small sample size of the study...

It will be determined based on the primary endpoint hypothesis of the overall trial, and cannot support older adults.

The individual statistical power of a group.

The second approach is a parallel queue design, where elderly people are placed in queues during the experiment.

This cohort may not be included in the main analysis of the study, but rather in conjunction with the main study cohort.

Parallel processing and separate analysis are performed. This design is more suitable for situations involving older populations and the main...

To study the differences among cohorts in dosing regimen, observed indicators, treatment duration, follow-up methods, or

When the timing, risk control objectives, etc., are not entirely consistent, or when the experiment...

Inclusion and exclusion criteria are insufficient to adequately consider both primary study cohort participants and older adults.

The elderly population is a necessary and important research subject, and direct data on their population needs to be obtained.

When receiving experimental data.

2. Independent trials in older adults

An independent elderly population trial refers to a trial that includes only elderly individuals.

The plan specifies a lower age limit (or allows for the setting of an upper age limit). Independent [activities] will be carried out.

Clinical trials involving older adults are designed to be better matched to the needs of this population.

Risk control in experiments can be more focused, data analysis is relatively simple, and experiments...

The results provide a more direct assessment of the benefits and risks of medication use in the elderly, but may also present challenges.

The slow recruitment process, when considered a pivotal study for drug registration, may affect the drug's performance.

Product development progress.

(iii) Collecting relevant data in post-marketing research

As a crucial part of the entire lifecycle management of drugs, post-marketing verification...

Worldwide research and quantitative pharmacology methods are used to continuously collect data on medication use in the elderly population.

This can effectively solidify the understanding of the efficacy and safety of medication in this population.

In addition, we will continuously update drug instructions and label information to further improve medication use for the elderly.

The availability and accuracy of relevant information will better protect the rights and interests of the elderly.

Drug safety and efficacy.

Common applications of post-marketing studies include: validating the efficacy of drugs in real-world clinical settings.

The actual effects of the environment on the elderly population further reveal the different characteristics within the elderly population.

Differences in treatment benefit between subgroups; support for its approval for use in general adults or certain age groups.

Medicines for the elderly population should be expanded to a wider age range (e.g., 85 years and older).

Extended use; optimization of dosing regimens, such as enabling individualized dose adjustments or using

Simplifying medication regimens or improving the medication experience, such as through drug use behavior research.

Conduct adherence assessments to identify medication misconceptions among the elderly and provide intervention measures; collect data...

Long-term safety or specific safety information, such as the discovery of rare or delayed adverse reactions.

And to monitor the cumulative toxicity of long-term medication in the elderly population. In special circumstances, [further measures should be taken].

Applicability assessments, such as evaluating the overall efficacy and risk of drugs in comorbidity management.

Risk assessment, or evaluation of its applicability in elderly patients with end-stage disease.

(iv) Application of modeling and simulation technology

In clinical research on innovative drugs for the elderly, there are various modeling and simulation methods.

It can be used in combination to provide safer and more effective drug treatment for the elderly.

The solution also significantly improved R&D efficiency.

Physiologically based pharmacokinetics

PBPK can integrate physiological characteristics, population characteristics, and active pharmaceutical ingredients.

And formulation characteristics, to analyze the pharmacokinetic behavior of drugs from a mechanistic perspective. In old

In population studies, the PBPK model adjusts physiological parameters in adult models.

Transform it into a model suitable for the elderly, or refine the model by adjusting system parameters.

Models for elderly populations of different age groups were established. These models can not only predict the age of the elderly...

Differences in pharmacokinetic dynamics between this population and the general adult population, such as drug clearance rate and its variability.

It can also support dosage selection and protocol optimization in clinical studies. Furthermore,

PBPK models also have significant advantages in predicting drug interactions when multiple drugs are used in combination.

It needs value.

Population pharmacokinetics (PopPK) can have

Effectively integrate data from multiple studies to establish a model for individual drug concentrations from a large number of sparsely sampled data sets.

Modeling, obtaining the typical values and variations of PK parameters in the population, and identifying factors affecting the population PK parameters.

The number of covariates is used to select dosages and simulate clinical trials, optimizing the administration of medications.

Medication plan.

The accuracy of modeling and simulation analysis depends on the level of scientific understanding and system parameters.

The reliability of the data. Currently, modeling simulations are being combined with experimental data from elderly populations.

This is a relatively ideal research strategy, which can save research resources and accelerate the research and development process.

It can also avoid the limitations of relying solely on predictive data. This is applicable in the development of drugs for the elderly.

By using multiple quantitative methods and prospective clinical trials in synergy, clinical trials can be further optimized.

Experimental design and decision-making. This involves integrating different models and analytical methods, combining the models...

By combining predicted and measured data, the model is continuously iterated and optimized to provide scientific support for subsequent decision-making.

in accordance with.

(v) Application of new technologies and methods

In recent years, artificial intelligence (AI) has been applied in pharmaceutical production.

Its application in the product lifecycle is becoming increasingly widespread, especially in drug research for the elderly.

In this field, advancements in related technologies are expected to accelerate the development of safe and effective drugs.

Based on the current application of AI in drug development, it is expected that AI will play a significant role in multiple stages.

It plays a vital role. For example, AI can integrate multi-source data (such as natural history, genetics, etc.).

Databases and clinical trial data can be used to deepen our understanding of diseases and can assist in clinical practice.

Predictive modeling of pharmacokinetics and exposure-response analysis in patients; applicable to patient risk assessment.

Risk stratification and management are achieved by analyzing patient characteristics (such as age, gender, and genetics).

Information, medical history, etc., can be used to optimize drug dosage and dosing regimens, and promote enrichment trials.

Design; it can also serve as an important component of drug development tools, through processing

Large-scale data (such as real-world data, digital health technology data), develop appropriate

Appropriate clinical trial endpoints to aid in the assessment of clinical outcomes and the identification of biomarkers.

In clinical trials, AI can also help monitor and confirm patient response to investigational drugs.

Adherence to the treatment plan is crucial to ensuring the reliability of trial data. This is especially important in post-marketing surveillance of drugs.

At this stage, AI can process and analyze large-scale real-world data, and promptly detect...

To better understand the adverse reactions of drugs and evaluate their long-term effects, especially for the elderly population.

Provide support for safe medication use.

When planning to use AI technology in drug development targeting the elderly, it is recommended that...

Prior to this, discussions were held with drug regulatory authorities regarding concerns, the use cases for AI models, and potential risks.

Thorough communication is essential. A detailed description of the proposed model architecture, data sources, and risks is required.

The training process and evaluation methods are designed to ensure the transparency and interpretability of the model.

In addition to AI technology, it is also encouraged in drug development targeting the elderly.

Explore the application of various other new technologies and methods.

IV. Benefit and Risk Assessment

Determine whether existing research designs and experimental data are sufficient to support the study of older adults.

Benefit-risk assessment typically includes: whether it is sufficient to detect the drug's effects on the elderly.

Differences in effectiveness and safety between the general population and the general adult population (general adult population has)

Efficacy and safety evidence are sufficient, and it has been approved for use in older adults.

(assuming the drug is approved), or whether there is sufficient evidence to support its use in the elderly population.

Efficacy and safety (approval in adults is generally not a prerequisite for approval in older populations)

hour).

If it is determined that the existing research design and experimental data are sufficient, but no detection was performed...

The differences in effectiveness and safety between the elderly population and the general adult population were measured.

Recommended clinical dosage regimens for adults and their corresponding efficacy and safety characteristics

Once this is clarified, it is acceptable not to adjust the dosage regimen for the elderly population.

However, the drug instructions can be based on the fact that older adults are more sensitive to drugs.

Appropriate warnings should be given in case of such situations, including based on pharmacokinetic data or model simulations.

The results showed that the indicators affecting metabolism and the corresponding potential effects on the elderly population were investigated.

The changes in characteristics are explained.

If it is determined that the existing research design and experimental data are sufficient, and the detection...

The differences in effectiveness and safety between the elderly and the general adult population are evident.

The recommended clinical dosage regimens for adults and their corresponding efficacy and safety characteristics are clearly defined.

After confirmation, it will involve judging the effectiveness and safety characteristics in the elderly population, from...

The decision on whether to adjust the clinically recommended dosage regimen and the drug's instructions for use is subject to change.

The information is reflected in specific indicator monitoring or risk management.

If it is determined that the existing research design and experimental data are sufficient, and generally...

When adult approval is not a prerequisite for approval by the elderly, the elderly population should be the primary consideration.

The generated trial data is the primary basis for determining the recommended clinical dosage regimen and administration.

The information generated from the drug's instruction leaflet. Although, this is usually obtained directly by the elderly.

Safety data regarding the risks of using drugs in a wider population after they are marketed.

Identifying more valuable individuals is possible, but considering the sample size and observational needs of older adults participating in the trial...

Limitations such as treatment duration should be considered when assessing the safety profile stated in the drug's instructions, referencing data from general adults.

It is also meaningful to supplement the entries and other content.

If it is determined that the existing research design and experimental data are insufficient, for example,

The overall clinical research did not include research objectives supporting medication use in the elderly population.

This includes those not aged 65 and above, and for whom existing data does not support modeling and simulation.

Analysis suggests that the quantity or quality of data on the elderly population may not support the reliability of the analysis results.

This also includes risk control when innovative mechanism-targeted drugs are used in special populations.

Due to considerations such as [the above factors], it is usually impossible to determine a clear clinically recommended dosage regimen for the elderly population.

If the opinions are unclear, it cannot support the generation of information regarding the use of drugs for the elderly in the drug instructions.

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