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CHOICE OF CONTROL IN CLINICAL TRIALS - ISSUES AND IMPLICATIONS OF ICH-E10

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Abstract

The ICH-E10 guideline on the choice of control group in clinical trials was a long awaited document. The concept paper gave reason to hope that it would give clear and harmonised guidance to an area, which has been very much disputed, including the burning issue of the role of placebo control. In the main, the final guideline was disappointing in spite of the long preparation time. In many respects it did not succeed to provide harmonised guidance across regions and it is not specific enough on a number of issues leaving the drug development stakeholders uncertain about what needs to be done. Examples of such issues are:

(i) the focus on individual studies rather than a whole clinical development program,
(ii) the choice of active control and the non-inferiority margin(d) in a non-inferiority trial,
(iii) the interpretation of "assay sensitivity",
(iv) the bias in favour of placebo-control,
(v) the failure of proposed alternative designs to resolve the unethical use of placebo.

The guideline does not acknowledge the gradual change of the clinical trial environment where placebo-controlled trials will be more and more difficult to conduct. This is driven by the existence of effective treatments in most therapeutic areas in combination with the new version of the Helsinki declaration. Sooner or later efficacy for a new drug will need to be demonstrated using active-controlled non-inferiority studies for most indication areas.

In order to meet this inevitable evolution efforts must be spent to further develop the methodology for non-inferiority trials, and to ensure that published meta-analyses provide the necessary information to allow the design of high quality non-inferiority studies in the future.

Key Words: ICH-E10; control group; placebo-controlled trials; non-inferiority trials; clinical trial environment; the Helsinki declaration

Introduction

The International Conference on Harmonisation (ICH) has developed a guideline entitled “Choice of Control Group in Clinical Trials” (ICH –E10), which was approved in July 2000 for implementation in all ICH regions, i.e. Europe, Japan and USA (1). The starting point for an ICH guideline is a concept paper stating the issues to be addressed and the objectives of the guideline. This was approved by the ICH steering committee for ICH-E10 in 1994 and thus it took more than six years to reach agreement among the members of the Expert Working Group.

This extremely long development time indicates the difficult nature of the subject. The title of the guideline may appear “innocent”, but it concerns very central questions such as the use of placebo controlled trials in relation to active control trials in proving efficacy for a new drug. It is well known that the three regions have very different perceptions regarding the role of placebo in clinical trials, where Japan by tradition has been very reluctant and US the most in favour. Therefore, it is an admirable achievement that a consensus guideline eventually was accomplished.

However, in order to accommodate the different opinions the guideline is not really a harmonised guideline, which was the objective of the concept paper. For example, it states that “this guideline does not address the regulatory requirements in any region, but describes what trials using each design can demonstrate”. This lack of harmonisation leaves the way open for a regional interpretation of the requirements for conducting clinical trials in each region to achieve a marketing authorisation.

During its development draft versions of the guideline were released for public consultation. EFSPI was very active in collecting comments from its membership for these reviews and a special workshop was organised together with Drug Information Association in Brussels in November 1999 to discuss the issues identified. Many of the concerns that EFSPI expressed in its comments were not resolved in the final version of the guideline. This is the background for this paper, in which we would like to revisit the ICH-E10 guideline and discuss the remaining deficiencies. These concern a number of interpretation issues and their implications for effective use of the guideline.

Another circumstance which has an impact on this discussion is the new version of the Helsinki declaration (2), the consequence of which is that placebo-controlled trials will be even more difficult to perform in the future when a proven effective treatment exists. Therefore, providing evidence of efficacy will necessarily have to rely more and more on non-inferiority trials without using placebo. An additional concern is whether ICH-E10 adequately reflects the gradually changing environment for performing clinical trials, and this also justifies a revisit of the guideline.

Main contents of the ICH/E10 guideline

The guideline starts with a description of the purpose of control group in a clinical trial and the importance of randomisation and blinding for avoiding bias in the treatment comparison. An account is given of different types of controls including placebo, no-treatment, dose-response, active control, external control, and multiple controls. The purpose of clinical trials is described distinguishing between those providing evidence of efficacy, i.e. a direct or indirect comparison with placebo, and those providing relative efficacy and safety information about a test compared to an active control. An indirect comparison with placebo can be achieved by showing superiority to an active control or by a non-inferiority study, where a test treatment is shown to be non-inferior to an active control previously shown to be superior to placebo.

The important concept of "assay sensitivity" is described in detail. "This is a property of a clinical trial defined as the ability to distinguish an effective treatment from a less effective or ineffective treatment" quoting directly from the guideline. Assay sensitivity for superiority and non-inferiority trials is the same, i.e. the trial should be designed, powered and conducted in a way that it is possible to show a difference between the effects of treatments of a pre-defined size when it exists. For non-inferiority studies, when the aim is to prove efficacy through an indirect comparison with placebo, an additional criterion is included in assay sensitivity. This is that historical evidence must exist showing that similarly designed trials of the active control regularly demonstrate superiority to placebo. A sufficient but weaker criterion is that similarly designed trials of a specific active treatment with similar effects as the active control reliably have shown an effect in the past. This criterion is called "sensitivity to drug effects". The purpose of this additional criterion is that a non-inferiority claim could not otherwise distinguish between equally effective treatments or equally non-effective treatments.

The guideline continues to give detailed considerations of the different types of control. For placebo-controlled designs a number of variations are given which are assumed to have less ethical difficulties, including add-on designs, early escape, limited placebo treatment, and randomised withdrawal designs. For each type of control a short account is given to the advantages and disadvantages of the particular design.

Finally, some guidance is given about the usefulness of specific types of control in various situations, and a flow chart indicating the basic logic for choosing the control in a specific trial.

Issues with the guideline

The ICH-E10 guideline addresses a complex and contentious research area and despite its long development time it contains a number of issues, which are discussed in this paper.

- *Lack of harmonisation – failure to fulfil the objectives of the concept paper*

In many respects the guideline is lacking regulatory harmonisation across regions – in several places reference is made to regional regulatory discretion. Rational drug development for international pharmaceutical companies requires the planning and conduct of clinical trials, which should be globally acceptable. Variations of trial designs or choice of control only to satisfy regional regulatory requirements expose patients unnecessarily to clinical trials and waste medical and financial resources. It also moves against the overall objective of ICH to allow eventually one common dossier for a new drug application.

- *Addresses an immature and still scientifically unsettled area*

Ideally a guideline should be a consolidation of the state of art for a mature research area. Recommendations should be founded in widely accepted theory and on extensive empirical experience. For the subject area covered in ICH-E10 this is unfortunately not the case. Examples of such controversial issues are the role of placebo in clinical trials, the role of non-inferiority trials for proving efficacy, the choice of the non-inferiority margin (δ) for such trials. It even introduces new ideas and terminology, such as “assay sensitivity” and “sensitivity to drug effects”.

One consequence of addressing an immature and scientifically unsettled area is that guidance necessarily becomes non-specific.. Many of the controversial issues are therefore left to the reader for interpretation.

- *Has focus on individual studies and not on a clinical development program of a drug*

The guideline has its focus on the design of an individual study. It would have been useful if the choice of control had been considered in the context of a complete clinical trial program, aimed at satisfying the requirements of the three ICH regions including both exploratory and confirmatory stages. Some guidance on the balance of the use of placebo and active controls during different phases of a program could have been given. This would be a major benefit to drug developers because it would clarify how some of the more specialised designs could be used as part of a package where large number of patients can only be treated in non-inferiority designs.

- *No specific guidance on choice of control for non-inferiority studies*

There is no specific guidance on the choice of the active control for non-inferiority studies. Which criterion should be used for the selection of the active control in a specific region or country? There are many possibilities such as the drug with the best proven effect, the drug with the highest current sales, the most recently approved drug, and the drug most similar in pharmacological profile.

Lack of guidance is also notable for the choice of active control in multi-national studies, an approach taken frequently for large therapeutic confirmatory studies. This can be particularly problematic when countries have different therapeutic practices and no active control drug has been commonly approved in all countries.

- *Interpretation of "assay sensitivity"*

The section describing the so-called assay sensitivity is very central for the guideline. Conceptually, this is a very valuable contribution that the guideline provided. This concept contains the criteria against which a non-inferiority study will be measured for success. As described earlier it has two components for an efficacy study using a non-inferiority design with an active control:

(i) Historical evidence of "sensitivity to drug effects" for the intended indication in placebo-controlled trials of the active control used with otherwise equivalent study characteristics to the planned efficacy study. This property could also be demonstrated using other controls than placebo and other active drugs than the selected active control. In this broader context it relates more to a property of the therapeutic area under study.

(ii) Appropriate study design and conduct capable of distinguishing an effective drug from a less effective or ineffective drug. This criterion includes the requirement that the study should be adequately powered to be able to exclude a pre-specified non-inferiority margin.

During the development of this guideline, this set of criteria has caused considerable confusion and the wording of this section has been revised several times. Originally, they were seen as two separate and independent criteria for a non-inferiority study. In the final version they are treated as one main criterion, assay sensitivity, with two related components. Part of the confusion depends on the choice of terminology, assay sensitivity does not directly associate to the indicated meaning of the concept.

- *No guidance on the choice of non-inferiority margin, "delta"*

In order to use an active control non-inferiority study for an indirect proof of efficacy against placebo a non-inferiority margin (δ) must be determined and agreed upon at

the design stage, as was discussed above. δ should reflect the maximum difference in favour of the active control in comparison with the test that would be regarded as clinically irrelevant. Some general methodological advice is given in ICH-E10 on this matter, but no specific quantitative guidance. No common regulatory standard seems to exist across regions and this absolutely critical component of a non-inferiority trial is still left to regulatory discretion in each region and country. The guideline even states explicitly: "Note that exactly how to calculate the margin is not described in this document, and there is little published experience on how to do this". Fortunately, this area will be addressed in a forthcoming Points to Consider paper from the European commission CPMP, which hopefully could give globally acceptable guidance on this matter (3).

- *Changes in clinical trial methodology*

The definition of assay sensitivity assumes that it is still possible to replicate trial designs, which were used historically to show that the control treatment was superior to placebo. But clinical trial methodology moves on. Diagnostic criteria improve. New and more relevant endpoints become established. The guideline suggests that the implications of this should be considered but gives no guidance on what a sponsor would need to demonstrate in support of the validity of a non-inferiority study. Such changes in trial methodology will also make the choice of the non-inferiority margin more contentious.

- *Lack of incentive to study excellence in non-inferiority trials*

The guideline claims that there is an intrinsic lack of incentive to study excellence in non-inferiority trials. However, there is always an incentive to conduct a study with low variability, also for a non-inferiority study. This will shorten the confidence interval for a treatment difference and thereby increase the possibility to show equivalence or non-inferiority.

It is the risk for a non-conservative bias that may create a problem, since sloppiness in conduct may have a tendency to bias a treatment difference to be smaller. However, the guideline does not discuss ways in which the clinical trialist can seek to maintain a high level of quality. All major pharmaceutical companies conduct studies using Standard Operating Procedures against which internal and external audits are often performed. Regular site monitoring visits can ensure quality data are recorded at trial centres. Assurance that the right patient population is selected can be provided by using a centralised randomisation system allowing entry criteria to be checked before randomisation. Compliance can be monitored using electronic devices, which record the timing of a dose. Assessment of trial endpoints can be standardised by training investigators or by using a central endpoint committee. The guideline would benefit from discussion of ways that quality can be maintained and demonstrated in non-inferiority trials.

- *The bias in favour of placebo controlled studies*

The current paradigm is that a placebo-controlled design is the gold standard for proving efficacy of new drugs in clinical trials. This conception is also strongly enforced in the ICH-E10 guideline. It is not our intention to challenge this basic standpoint, placebo-controlled trials have their obvious place in drug development as long as they can be justified from ethical viewpoints. We also recognise that active-controlled non-inferiority trials are less credible than placebo-controlled trials for proving efficacy defined as superiority over placebo. However, the guideline appears to underestimate some of the problems associated with such trials. It mentions a number of potential drawbacks with the use of placebo in clinical trials including ethical concerns, patient and physician practical concerns, generalisability issues, but the general tone is somewhat uncritical to these concerns. In reality all these concerns may cause more problems than are indicated in the guideline, in particular the ethical aspects in face of the changing clinical trial environment, which will be addressed further below.

There are a number of other drawbacks with placebo-controlled trials, which can weaken their usefulness. One drawback concerns the increased difficulty in maintaining blinding in a placebo trial compared to an active control comparison. The importance of maintaining blindness is stressed in the guideline itself because failure to do so may lead to bias in the evaluation of both efficacy and safety. For an active control non-inferiority study with a control treatment similar in pharmacological profile to the test treatment, the risk of gradually unblinding the study may be considerably less.

Another circumstance worth mentioning is the risk for unequal variability in the treatment groups in a placebo-controlled trial, which may reduce power. It is not uncommon that patients treated with placebo exhibit larger variability compared to patients treated with an active treatment due to the existence of subgroups of placebo responders and non-responders.

The use of a placebo control may also severely limit the patient group that can be entered into the trial and some design features like the length of treatment. It may be necessary to include only patients with mild severity or those with early stage disease not previously treated. It may also limit the choice of investigator to those with appropriate facilities to handle potential deterioration in placebo patients. Showing a difference from placebo in such a trial may provide little information about how the test treatment will fare in a wider population of patients. It may be relevant in the context of a drug development programme and this is one reason why it is disappointing that the guideline focuses only on single trials.

- *Alternative designs leave the placebo issue unsolved*

The guideline gives a number of alternative designs which could be considered if a traditional placebo-controlled trial is deemed not feasible. These include

(i) Three armed design using test, active control and placebo

The three armed design is obviously not an alternative in a situation where placebo cannot be used for ethical or other reasons. It is particularly useful when the primary objective is to assess the relative efficacy/safety of a test

and an active control. This design offers the possibility to evaluate the appropriateness of the chosen design through a comparison between the active control and placebo. If this is not significant a failed comparison between the test and placebo could be due to a flawed design rather than an inefficient test treatment.

(ii) Unbalanced assignment of patients to placebo and test treatment

By this design it is implied that a smaller number of patients could be assigned to the placebo group compared to the test treatment group. For a continuous outcome variable the loss of power will be fairly small provided the unbalance is kept within the range of 2/3 – 1/3. However, even if the total exposure to placebo is reduced in this design the fundamental ethical issue for an individual patient is unsolved.

(iii) Dose-response

The usefulness of a dose-response study for proving efficacy implies the use of a sub-optimal dose. If such a dose is deliberately chosen in order to mimic a placebo as close as possible the ethical dilemma is still remaining. If not, this approach could seriously be considered as a realistic alternative in many situations.

(iv) Add-on design

This design denotes a placebo-controlled comparison on top of a standard treatment given to all patients. If the improvement that is achievable in addition to that obtained from the standard treatment is small, the size of such trial may need to be very large. Even though the test versus placebo comparison can be shown to be unbiased, the effect size of the test will most likely be underestimated due to a ceiling effect. Furthermore, since this is a reduced factorial design any interaction effects will not be possible to evaluate.

(v) Early escape

The early escape design using a placebo control allows a patient to be withdrawn from the study as soon as a predefined negative efficacy criterion has been attained. The patient could then be switched over to another therapy, including the test treatment if appropriate. The time for withdrawal is then used as the primary outcome variable. In some instances this design could give preliminary evidence of efficacy, but the scope of such a study will usually be very limited. Most likely, it will be necessary to confirm the efficacy in a non-inferiority study using an active control.

(vi) Randomised withdrawal

This design means that all patients are given the test treatment during a pre-specified time after which they are randomised to either test or placebo

treatment. The actual treatment comparison is based on differences recorded after a relevant treatment period upon randomised withdrawal. If the test treatment is effective and sustainable the comparison will be based on the deterioration of those treated with placebo in this design. The more deterioration the clearer evidence is. Apart from the "advantage" to be treated with the test treatment during the run-in phase it is doubtful whether this design resolves any ethical concerns. In addition, this supposes that the test treatment is already proven to be effective, otherwise this design would not be ethical.

In summary, the alternative designs offered in the guideline may in some cases be useful. As has been pointed out in the above they do not always resolve the fundamental ethical issues. Furthermore, the research questions addressed in some of these designs are not those of primary interest, even though they formally may have the potential to provide evidence of efficacy.

The change of the clinical trial environment

The environment for undertaking clinical trials in drug development is gradually changing. One important element of this change is the perception of the role of placebo. In the light of the continuing increase of new effective treatments, the use of placebo in clinical trials is challenged by the medical community including ethics committees and also by common interest groups of patients such as those with HIV. The internet provides a vehicle for greater patient awareness which will accelerate this trend. This has become especially evident through the new version of the Helsinki declaration (2), where there is a sharper wording with respect to the use of placebo in clinical trials.

The relevant sentence addressing placebo reads now: "The benefit, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists". A similar statement has been included in earlier versions of the declaration, but it is a general understanding that the wording of the new version implies a more evident discouragement to the use of placebo when a proven effective and safe therapy exists. A common interpretation of this statement of the Helsinki declaration, most clearly expressed by the drug regulatory authorities, is that it cannot be taken literally, because this would essentially stop all drug development under the current placebo paradigm (4,5). The central theme of the argument is that only for life-threatening diseases or diseases which could cause irreversible disability if not adequately treated should placebo-controlled trials be excluded. In all other situations these could be used, provided that informed consent is given by the patient, and that a delay in active treatment does not affect the patient´s long-term health. However, this interpretation has also been challenged, for example in (6).

Even though the declaration is open for interpretation, for example with respect to what is meant by a proven therapy, it constitutes a pointer to the direction in which

drug development is moving. It is probably only a question of time before placebo only can be used in early phase studies or short-term mechanistic proof of concept studies. Sooner or later it will be practically impossible to perform placebo-controlled studies for therapeutic confirmatory purposes. Indeed, it is already now increasingly difficult to conduct placebo-controlled studies in a number of indications, such as Alzheimer´s disease, multiple sclerosis, major depressive disorder, just to mention a few from the CNS area. For all these indications there exist therapies "proven" by regulatory authorities, even though these therapies have moderate effect size and have not regularly demonstrated efficacy against placebo. This circumstance puts the drug developer in a "catch 22" situation. The conditions for using non-inferiority designs to prove efficacy may not be acceptable to the regulatory authorities according to their current policies as expressed in ICH_E10 guideline, and investigators/patients/ethics committees will not accept a placebo-controlled study.

Implications for drug development

This change of the clinical trial environment has important implications for drug development. There will be increasing difficulties in balancing regulatory requirements against ethical considerations with placebo-controlled trials. This may result in inappropriate compromises in study designs and patient selection, which ultimately will endanger a scientifically sound drug development.

Too stringent requirements for non-inferiority studies will imply that superior efficacy over the standard treatment will be the challenge that drug companies have to face. This will obstruct valuable incremental research, as it will be virtually impossible to benefit from small improvements of a new drug compared to existing therapy. It is true that this policy will prevent a possible downward "creep" in efficacy, but it will also imply that improvement of therapy by degrees will become impossible. The experience from many therapeutic areas is that incremental improvement over standard therapy is the normal situation and that such improvements accumulated over time become valuable for patients. Very rarely can we expect to get new treatments on the market, which are dramatically better than existing treatments.

Such incremental improvements may not always concern efficacy. It is not uncommon that the efficacy of the standard treatment is obtained at the expense of safety or tolerability. An obvious development strategy in such areas would be to develop a new drug with improved safety or tolerability while retaining as much as possible of the efficacy of the standard treatment. It would be unfortunate if conditions for drug development would render it more difficult to achieve such improvements.

What is needed for the future

- *Further methods development in the area of non-inferiority studies*

  Our prediction is that non-inferiority studies will be the standard method to demonstrate efficacy in the future. This future may be more or less distant, but all stakeholders in drug development, whether they are regulatory authorities, drug companies, or investigators/patients, must prepare themselves for this evolution. It is therefore important that further efforts are spent to develop the methodology with respect to design, analysis and interpretation of non-inferiority studies. This is essential in order to be able to explore fully the opportunities and pitfalls with such studies. We also need to understand better how the inferiority margin should be set and how the historical evidence should be assessed and used in the design of non-inferiority studies.

- *A knowledge base*

  Ideally regulators should stimulate the creation and publication of meta-analyses, which include all essential information of acceptable standard treatments for use in non-inferiority studies. These publications should contain information about placebo-controlled studies, design characteristics, indications, patient selections, effect sizes, variability measures etc. Eventually, also active controlled studies should be included in this activity, because in the long run data from placebo-controlled studies will not be available.

- *A consensus about choice of control and d for non-inferiority studies*

  International drug companies develop new drugs for global marketing authorisations. The vision of the ICH is to allow one and the same dossier to be submitted to all regulatory authorities. For this to be possible regulatory authorities need to reach consensus about the choice of control and δ for non-inferiority studies. Not only the principles for this choice should be agreed but also which standard treatment could be acceptable and the size of δ for commonly used outcome variables.

- *Clear guidance on how assay sensitivity could be demonstrated to satisfy regulatory requirements*

  The ICH-E10 guideline gives some general advice on how assay sensitivity could be demonstrated. Preferably, this guidance should be more specific with regard to how this critical criterion could be satisfied. Until further research has been performed in this area and the above mentioned meta-analyses are available drug companies need to negotiate with each individual regulatory authority for an acceptable approach. Needless to say, this is very unsatisfactory in a global environment.

- *Post-authorisation studies to support efficacy similar to pharmacovigilance for safety and tolerability*

Current legislation in all ICH regions requires that efficacy is convincingly demonstrated for a new drug before it could be marketed. It is required that safety and tolerability should be reasonably well demonstrated, but it is understood that this cannot be unequivocally demonstrated within the framework of a clinical trial program. In order to monitor safety and tolerability of a new drug on the market different pharmacovigilance systems are in place to capture adverse findings. If evidence of efficacy will have to rely more and more on non-inferiority studies in the future there might be a risk that less effective drugs will be authorised for marketing. It may be necessary to conduct further studies supporting the conclusion of efficacy using observational databases or post-marketing trials.

Conclusions

In many respects the ICH-E10 guideline has not succeeded in the ambition to provide harmonised guidance across regions, and the guideline is not specific enough on a number of issues leaving the drug development stakeholders in uncertainty about what needs to be done.

The guideline does not acknowledge the gradual change of the clinical trial environment where placebo-controlled trials will be more and more difficult to conduct. Sooner or later it will be unevitable that efficacy for a new drug will need to be demonstrated using non-inferiority studies in most indication areas.

In order to meet this inevitable evolution efforts must be spent to further develop the methodology for non-inferiority trials, and to establish a publicly available knowledge base containing necessary information to allow the design of high quality non-inferiority studies in the future.

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