Questions and Answers by the CTFG on clinical trials
Answers to frequently asked questions

The CTFG proposes answers to questions frequently raised by sponsors of clinical trials on medicines in Europe.

Questions can be asked to national competent authorities whose representatives can forward them to CTFG in order to get, as much as possible, a harmonised position.

These Questions and Answers reflect the general opinion of CTFG but can in no way be considered as mandatory.

Actions and initiatives on individual clinical trials need to be authorised by all concerned instances in each member state (competent authorities and Ethics committees).
Follow-up of patients after a clinical trial has ended

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1. General

In November 2009, the issue of follow-up of patients after a clinical trial has ended was discussed in a public workshop between CTFG and industry representatives. Clinical trials may reach the point of final analysis when individual patients may be still benefiting from the treatment. Sponsors may want to close the trial from an operational perspective, while maintaining these patients on the investigational treatment.

2. What are the different options to provide treatment to individual patients when a trial has ended?

There are several ways to continue access to the treatment:

- Keep the clinical trial open (and update the definition of end of trial)
- Roll patients into a «follow-on» protocol (adding a period to the initial CT by substantial amendment)
- Roll patients into one dedicated «catch-all» protocol (grouping patients from different trials)
- Compassionate use

3. What is CTFG’s preferred option?

As stated, each trial should be evaluated differently by the sponsor. Some points should be taken into account:

- not every Member State has the notion of compassionate use in its legal framework, and the application for compassionate use can vary between Member States
- changing the definition of end of trial (thus prolonging the clinical trial) is only interesting in very specific cases. The disclosure of study results in a timely manner (e.g. through interim study report) and the correct reporting of the end-of-trial need to be ensured in this instance.

The use of the clinical trial framework (by putting in place extension trials or catch-all trials) would in general be the preferred option.

4. What about the objective of a catch-all / extension trial?

The scientific objective of catch-all protocols and extension trials can for instance be the long-term safety follow-up. A scientific objective should exist. The trial should be structured to efficacy and safety in light of duration, inclusion criteria, end points,…

An extension trial can be ended before the moment of marketing authorisation if a scientific rationale exist. The end of trial should not be defined as the time of the marketing authorisation.

Generally speaking no new patients should be included in these catch-all / extension trials: the participation to previous trials with the IMP should be an inclusion criterium.
1. What is the definition of a novel-novel combination?

A novel-novel combination is a combination of two or more active substances that have not received any marketing approval and will be tested in one or more clinical trials. It can be the intention to develop the products as a combination only or as a combination and as monotherapies. Although in particular early phase developments (the first time a combination will be used in humans, high risk entities) should receive particular attention, all combinations of products that have not reached marketing authorisation are envisaged.

2. What are the reasons for this type of studies?

The separate IMP’s may not have sufficient therapeutic effects or the combination of two or more different activities may enhance each others therapeutic effect. In most cases different targets are affected by the different substances. Such combined activity is for instance expected but not exclusively limited to the treatment of tumours and infective diseases.

This type of studies may be conducted if there is a scientific rationale for the use of two different drugs and if possible there should be evidence in a mechanistic non-clinical model showing additivity.

FDA recently published a draft guideline and stated that co-development should ordinarily be reserved for situations that meet the following criteria:

- The combination is intended to treat a serious disease or condition.

- There is a compelling biological rationale for use of the combination (e.g., the agents inhibit distinct targets in the same molecular pathway, provide inhibition of both a primary and compensatory pathway, or inhibit the same target at different binding sites to decrease resistance or allow use of lower doses to minimize toxicity).

- A preclinical model (in vivo or in vitro) or short-term clinical study on an established biomarker suggests that the combination has substantial activity and provides greater than additive activity or a more durable response (e.g., delayed resistance) compared to the individual agents alone.

- There is a compelling reason for why the agents cannot be developed individually (e.g., monotherapy for the disease of interest leads to resistance and/or one or both of the agents would be expected to have very limited activity when used as monotherapy).

CTFG finds this an interesting and useful document, but would like to develop further experience with the submitted CTA’s to broaden or tighten this view. A dedicated subgroup has been created.
3. Are there any obstacles or special conditions for approval of clinical trials with novel-novel combinations?

Safety issues, added activity and any clinical experience should be sufficiently addressed in the CTA. Obviously, if there is clinical experience with the individual compounds, this may influence the need for non-clinical data. The main issue to be addressed is whether the non-clinical data should be obtained for the individual compounds, the combination, or the individual compounds and the combination. Also, what doses should be tested in the animal models if data on the combination are expected needs to be justified. In many cases the dosing schedule should also be considered in relation to the expected clinical dosing schedule. It should also be considered that the route of administration could be different. An issue could also be the desired flexibility to adapt administration (dose, schedule, route) independently in the early clinical trials. How these non-clinical findings will be taken into account in the clinical plans will of course be looked at and the determination of the starting dose(s) and the need to administer single compounds before or in addition to the combination will be considered.

4. Are fixed combinations of new active principles possible?

This might be possible but then additional issues with regard to CMC might be raised. The fixed combination would be less flexible in the choice of doses that can still be adapted if the products are administered apart. The testing of novel-novel combinations may ultimately lead to the development of fixed combinations, once doses, dosing schedules, route of administration etc. are established.

5. What are CTFG conditions for approval?

The preclinical data should be sufficient to justify the combination at certain doses and with certain dosing schedules. This will be judged on a case by case basis. The existing guidance on combination products may be useful and in particular the ICH M3 (rev. 2) guideline should be consulted. In addition there is also information available on combinations in the ICH S9 guideline with regard to treatment of advanced and metastatic cancer. Since the requirements may not always be clear and depend on the case, based on the supporting evidence on toxicity and efficacy, it would often be fruitful for the sponsor to obtain scientific advice from national competent authorities and/or CHMP at EMA. A working subgroup within CTFG is working on a position regarding harmonized requirements and evaluation of CTA’s with combinations of novel substances. It is important to come to a similar interpretation between Member State competent authorities of existing guidance (ICH M3, ICH S9, guidance on fixed combinations, draft FDA guidance) and to propose new guidance in concert with working groups at EMA when needed and based on the experience acquired. In the mean time, industry is also invited to provide input on specific points they would want to be harmonized. If clinical trials will be conducted in 2 or more member states it is strongly recommended to enter a VHP procedure.

6. Are ATMP included in this statement?

Since such products are new and expected to have their own particular development strategies and difficulties, CTFG prefers to treat ATMP on a case by case basis. There are no known examples yet of novel-novel combinations, which is another reason to exclude these from the
present statement. This does however not mean that in the future this cannot be reconsidered and adapted in line with knowledge and experience that will be available then.

7. How will background treatment be taken into account?
The background therapy that may be used with the novel-novel combination in the case of for instance cancer treatment may be another complicating factor. In general background treatment will be taken into account similarly as is the case with one novel IMP.
Questions & Answers concerning IPD

1. What is the definition of Integrated Protocol Design (IPD)?

IPD is one study protocol which contains 2 or more parts, with a concrete scientific rationale for the combination. Within this protocol details are predefined, e.g. the definition of dose or dose interval, for a later part, which need to be concluded from data generated in a previous part of the study.

Examples for IPD are various combinations of trials typically within one phase I or II or transition trials phase I/II; for example regarding Phase I: single dose and escalation, multiple dose and escalation, dosing interval, food interaction and so on.

2. Does it concern only early development studies in oncology?

It concerns mainly early development studies, e.g. phase I studies in healthy volunteers, phase I/II an phase II studies. IPD studies are more frequently used in oncology trials but are not restricted to this indication.

Adaptive design trials, which have a predefined statistical hypothesis to be adapted during the study, are usually studies in later development such as in Phase II/III or III. Adaptive design studies are not within the scope of this Q&A document.

3. How to progress from one part to another within a Phase I IPD?

1) Within the submitted clinical trial application documentation, the following issues and conditions, should be addressed sufficiently. If appropriate, discussion of criteria and/or justification of deviations should be provided.

   a) a concrete scientific rationale for the combination design.

   b) Specifications in the protocol:

      ▪ No changes in the formulation of IMP during the CT
      ▪ Safety margins are discussed and considered sufficient
      ▪ If pre-clinical data are not sufficient to cover the entire study plan, a detailed plan for submission of additional pre-clinical documentation is provided and these data will be submitted as a substantial amendment (SA)
      ▪ A defined maximal dose or a maximal exposure
      ▪ Clear rules for stopping dose escalation
      ▪ Clear description of each part of the protocol
      ▪ Detailed decision criteria and time of decision to allow progression to further part
      ▪ Definitions of responsibilities for progression to ensure unchanged benefit/risk of the study
      ▪ A Data Safety Monitoring Board for monitoring and for decisions is installed and its composition and remit are provided

   c) Information in the cover letter:
The cover letter should specify which type of IPD is submitted and give information in which country/countries which part of study will be done or has been already approved.

II) Provided the previous conditions are fulfilled, and

a) the pre-specified criteria to progress further are met and the benefit/risk remains unchanged, CTFG considers that there is no further requirement for NCA(s) to be notified to progress from one part to the next.

b) the pre-specified criteria are not met, progression can only be achieved after NCA(s) authorization of a submitted Substantial Amendment (SA).

4. Are ATMP included in this statement?

No. ATMP are not considered suitable for the IPD approach at this time. Experience has to be gained.

5. If IPD also involve transition phases, such as phase I/II, are the criteria the same?

For the moment, the progression from one part and phase to another part and phase will normally be possible only after submitting a SA, which needs to be authorized by the NCAs prior to proceeding to the next phase of the study. This will however be considered on a case by case basis. The outcome could be also a request for the submission of 2 CTAs. CTFG is going to harmonise the process further in the future after gaining and sharing experiences within the Member states. For this reason CTFG has established a project leader for IPD. CTFG highly recommends that if these studies are supposed to be done in two or more member states they are submitted through the VHP.
Abbreviations

ATMP : Advanced therapy medicinal product
CT : clinical trial
CTA : clinical trial application
CTFG : clinical trials facilitation group
CMC :
EMA : European Medicines Agency
FDA : Food and Drug Administration
IMP : investigational medicinal product
IPD : integrated protocol design
NCA : national competent authorities
Q & A : questions and answers
SA : substantial amendments