LEAGUE OF EUROPEAN RESEARCH UNIVERSITIES

LERU note

June 2012

Clinical trials and Horizon 2020

This note[1] considers the difficulties LERU members have experienced when conducting clinical trials[2] as part of FP7 Co-operation and the Joint Technology Initiative's Innovative Medicines Initiative (IMI) projects. This paper examines these issues and makes a series of recommendations for actions by the European Commission (EC) to improve the provisions for conducting clinical trials in EU projects. Such actions would be very timely, not only in readiness for the beginning of Horizon 2020 in 2014, but also in light of the current revision of the EU Clinical Trials Directive.

Current situation

In FP7 there are few EC guidelines on how to administer clinical trials as part of research projects conducted under the Health priority in the Cooperation programme or under IMI and consequently practices vary widely. It is of particular importance to improve this situation owing to LERU's experience of the increasing number of clinical trials conducted in FP7 as the programme has progressed. Furthermore, the Horizon 2020 plans for the Health, demographic change and well-being societal challenge clearly foresee the need to include clinical trials.

Despite the current variability in conducting clinical trials as part of FP7, there are common difficulties experienced by LERU members, regardless of international, national and local practices in managing clinical trials. These problems can be broadly defined as either administrative or financial and will be considered in turn below.

1 The note is based on a consultation among the LERU Community of European Research Project Managers (ERP). The main author of the note is Carole Meads, Senior Negotiator, European Policy at Imperial College London.

2 Defined as a set of procedures in a medical research project that are conducted to allow safety and efficacy data to be collected for health interventions.

1. Administrative problems

The principal administrative difficulty LERU members have faced is how to include partner hospitals and/or clinics in the Grant Agreement. In the UK many universities have a research governance agreement or similar collaboration agreement with their main partner hospital National Health Service (NHS) Trust. Some have a single Joint Research Office. Notwithstanding these close working relationships, the university and the hospital remain separate legal entities. To complicate the matter further, there is usually a need to include multiple hospitals or clinics in the trial procedure and not simply the hospital with which the university has a close relationship. These hospitals or clinics may be in the same country as the university concerned or they may be elsewhere in the EU or in third countries, including developing countries.

In theory, there are three potential legal choices for including partner hospitals or clinics in FP7 Grant Agreements: full partner; third party or sub-contractor. The advantages and disadvantages of each are discussed below.

(i) Full partner

Usually the hospitals or clinics are simply recruiting patients to participate in the trial and are thus not themselves actively conducting research as part of the project. It is therefore not clear why a hospital would need to be a full partner in the Grant Agreement as it is not research active. Furthermore, in most countries the hospital financial management systems are set up to meet the governmental national health requirements and are often not compatible with those of a FP7 full partner, i.e. hospitals are frequently unable to identify their direct costs on a project basis, a further factor arguing against them being a full partner in an EU-funded project.

However, in many projects a university partner hospital is included as a full partner (see also Financial problems section below) although practice is not consistent either between universities or within FP7 projects from a single university. Much seems to depend not only on the specifics of the project but on the opinion of the EC project officer in question. It has, however, been suggested by the European Commission that a hospital should always be a full partner if its funding reaches €100,000 - €150,000. If so, the EC should disseminate this information widely in order to clarify the process. Whilst the full partner option is viable if each university requires the services of only its partner hospital in order to conduct the clinical trial, it is clearly not an option if a large number of hospitals or clinics are required for patient recruitment. This is because the EC is reluctant to allow large numbers of partners in a single project, the maximum number again often seeming to depend on the viewpoint of the particular project officer in charge.

Even if included as a full partner, there are still financial problems for hospitals and clinics in participating in EU clinical trials; these difficulties are addressed in the financial problems section below.

(ii) Third party

It would seem at first sight that the best approach would be to include each hospital as a third party using Special Clause 10 'Third Parties Linked to a Beneficiary' of the FP7 Grant Agreement. This may well be an appropriate course of action for those hospitals or clinics closely associated with the university in question; indeed, LERU members have used this mechanism successfully in such cases. This does, however, increase the risk for the university which has to bear legal responsibility to the EC and to the rest of the consortium for the linked third party's performance. Although the hospital is thereby able to claim its eligible costs under the general financial provisions of FP7, provided its financial systems meet the EU requirements, it still experiences a financial shortfall as explained in the financial problems section below. Furthermore, it is clear that this approach is not appropriate in situations where there are many hospitals or clinics involved in the trial on an ad hoc basis, especially if they are outside the EU, as it would be very difficult for a university to manage the administration of their participation in this way and to guarantee that they all abide by the provisions of the Grant Agreement. Furthermore, it is unlikely that the EC would accept in the Grant Agreement a large number of third parties linked to a single university.

(iii) Sub-contractor

As sub-contracting is not allowed for core activities in FP7 projects it is clearly open to interpretation how 'core' the recruitment of patients is to a research project incorporating a clinical trial. For instance, when a hospital or clinic is only recruiting patients according to a protocol to which it has not contributed in designing and will not be involved in data and safety monitoring or translational research with human material derived from such a trial, such an involvement is obviously not 'core' research in the normal meaning of FP7. Yet on the other hand sub-contracting in FP7 is envisaged only for minor services; this also does not seem applicable in the context of clinical trials as without the recruitment of patients the trial could not proceed.

Nevertheless, subcontracting is the route that some LERU universities have taken in most of their FP7 projects involving clinical trials. This decision was taken on the basis that patient recruitment is a service, not research per se, and that the resulting data are analysed by university staff who are thus providing the intellectual input to the process. Again, however, the problem arises of how to incorporate multiple recruiting centres into a FP7 project. Furthermore, some LERU members have been instructed by the Commission that the normal procurement rules of the institution should be followed in the case of subcontracting; these can be very difficult to align with the project requirements of patient recruitment at specific geographical locations. The principal problem with subcontracting, however, is financial and is addressed in the financial problems section below.

(iv) Additional administrative difficulties

The lack of clear Commission guidelines presents further administrative difficulties for universities involved in clinical trials. For example, there may be differences in interpretation as to whether a trial constitutes a Clinical Trial of Investigational Medicinal Products (CTIMP) in a particular country. This can lead to issues with who the sponsor of the trial should be if the trial is not a CTIMP. Usually, each country would sponsor the trial devised by the FP7 collaborators but in the UK this instance means that there is uncertainty over who designed the protocol and who should be responsible for it. UK universities normally insure protocols designed by their own employees, but like to see confirmation from all other partners that their insurer is aware that the university is a contributor so as to avoid problems such as double insurance.

In addition, the EC does not appear to appreciate fully the question of insurance in developing countries and thus does not realise the potential detrimental impact for EU universities. The developing countries' participation may be crucial for the project's potential success but, because of their lack of infrastructure and related governance problems, such countries frequently have difficulty in obtaining the requisite insurance for clinical work. Such work is not included in universities' or associated hospitals' standard insurance policies and thus they have to purchase additional insurance to allow the clinical work in developing countries to proceed. This clearly has a negative financial impact on EU universities and is a further disincentive to participation by them in clinical trials funded by the EC.

Further administrative difficulties relate to the fact that the clinical trials often take place towards the end of the project so there are a number of unknown factors at the beginning which make it difficult to estimate costs accurately and to negotiate specific clinical terms in the Consortium Agreement. This problem is further exacerbated by the fact that model Consortium Agreements do not contain any wording for clinical work so there is no common view on how to address these issues. It is also important to remember that some trial centres may be very small (e.g. a general practitioner's surgery) and would have neither the management nor accounting practices in place to enable them to comply with the EC's regulations. Such trial centres typically have no experience of EU contracts and this adds to the complexity and time required to manage their involvement.

2. Financial problems

The FP7 financial rules on subcontracting have presented a major problem to LERU universities in current clinical trial projects. This is because subcontracts are reimbursed only at 75% of direct costs with no indirect costs but hospitals and clinics will normally participate only if they receive 100% cost recovery. This means that the university is making a 25% loss on the costs of each hospital or clinic involved in the trial. This situation is clearly not sustainable for the long-term or wide participation of universities in FP7 or Horizon 2020 clinical trial projects; this in turn begs the question of how such trials can be conducted successfully without the participation of EU leading medical universities. Whilst LERU universities are happy to accept the 'co-funding' principle for reimbursement of their own costs, the cur-

rent rules mean they are actively subsidising hospitals and clinics to participate in EU clinical trials; this is neither acceptable nor fair.

Financial problems remain even when hospitals and clinics are a full partner in a EU clinical trial project. This is because they rightly expect their costs to be reimbursed at 100% of direct costs but the FP7 rules allow only for a 75% direct cost and 65% indirect cost recovery. This means Member States' national health systems are subsidising the costs of EU clinical trials which is neither acceptable nor sustainable. Moreover, there remain important differences between Member States as to which clinical interventions can be considered as 'standard-of-care' and can be reimbursed by the applicable health insurance mechanism.

Furthermore, trial costs are dependent on the number of patients recruited by each centre and are therefore difficult to estimate accurately at the onset of the project. This often leads to the need for continuous redistribution of finances between different partners and centres during the project as actual recruitment may vary widely from planned recruitment. Such a process leads to a great increase in project administration and associated costs for the university. In some cases it is necessary to add new hospitals or clinics in order to achieve recruitment targets and this is difficult to achieve in FP7. One possible way forward would be to include a protocol as part of Annex I for those trials that involve a substantial intervention on patients and a relation with the standard-of-care procedure and costs. However, as this will not be a solution in many cases, an alternative could be a two-step procedure, with a first deliverable being a protocol which then serves as a basis for budgeting the second phase.

LERU universities have also experienced financial losses in EU clinical trials owing to the FP7 rules on receipts to the project. In several instances the project officer has deemed partner hospital resources to be receipts to the project leading to a further financial shortfall for the university.

Recommendations

It is clear from the above that there is an urgent need for the European Commission to consider in detail the current problems with conducting clinical trials in FP7 and to address the issues now if clinical trials in Horizon 2020 projects are to be successful. LERU suggests the following actions by the EC would be helpful in improving the situation:

1. We would welcome **clear EC guidelines on conducting clinical trials as part of FP7, IMI and Horizon 2020 projects**. The preparation of these guidelines should involve the Commission officials participating in the current revision of clinical trials legislation. The guidelines should cover all administrative and financial aspects and include in particular guidance on how best to include trial recruitment hospitals and clinics in the Grant Agreement, legal sponsorship of the trial, insurance and the transfer of human samples. LERU would welcome the opportunity to liaise further with the EC on these matters.

2. We recommend also that the **EC runs better training for its own staff** on incorporation of clinical trials in FP7 and Horizon 2020 to ensure consistency of approach between project officers.

3. We are concerned that the current wording on third parties in Article 19.5 of the Horizon 2020 Rules for Participation perpetuates the problems of conducting clinical trials in EU projects and wish it to be amended. Similarly, the present wording of Article 22.2(a) on receipts to the project is highly problematic. We recommend that **EU policy makers specifically consider the case of clinical trials when producing future drafts of the Rules for Participation.**

4. LERU recognises that some flexibility will be needed owing to national differences in the relationships between universities and hospital health systems and also owing to differences in legislation in some areas. We suggest that a possible way forward, which would provide both clarity and flexibility, would be to **introduce a special derogation for conducting clinical trials under Horizon 2020**; Article 47 Specific Provisions of the Rules for Participation would be the appropriate place for such a provision.

5. It is crucial that universities and hospitals do not suffer a financial loss from participating in EU clinical trials. Systems must therefore be introduced that allow **100% cost recovery for parts of the clinical trial that are conducted in hospitals or clinics**. Whilst it is essential that this problem be rectified before Horizon 2020 begins, LERU would welcome a resolution to be applied during the rest of FP7. Clearly, if the proposed Horizon 2020 funding reimbursement of 100% of direct costs (and 20% indirect costs) goes ahead, this will alleviate the financial problem in the cases where hospitals and clinics are full partners in the project.

6. In line with the much-heralded simplification and more appropriate trust/checks balance of Horizon 2020, it would be helpful if **hospital flat rate costs for extra costs which are not standard-of-care costs were acceptable for clinical trials**. One possibility would be for the project partners to produce a consortium-level trial budget (i.e. not assigned to specific partners at proposal stage) with a flat rate per patient. Such flat rates would have to vary from clinical trial to clinical trial depending upon the complexity of the patient tests and the balance of invasive or non-invasive procedures. This flat rate could be approved by the Commission during grant agreement negotiations, the budget distributed between partners according to the numbers of patients successfully recruited and the flat rate used to report clinical trial costs.

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LERU Facts and Figures

- Together LERU member universities account for more than 450,000 students and more than 50,000 PhD students.
- Each year about 50,000 master degrees and 11,000 doctorates are awarded at LERU universities.
- The total research budget of LERU's members exceeds € 5 billion.
- About € 1 billion is granted by research councils, while approximately € 1.25 billion comes from contract research.
- The total sum of research grants from EU projects to LERU universities is approximately € 260 million.
- Approximately 20% of ERC grants have been awarded to researchers at LERU universities.
- More than 225 Nobel Prize and Field Medal winners have studied or worked at LERU universities.
- 50,000 academic staff and 52,000 non-academic staff work at the member institutions (hospital-only staff not included).

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LERU notes are short, timely statements providing concise analysis and specific advice in response to a pressing issue related to European research and higher education policies. They are often a product of LERU's standing engagement with certain issues and a result of intensive consultation among experts from the LERU universities.

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